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DIVISION OF NARCOTIC DRUGS

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Problems of competence in international law with regard to the punishment of narcotic drug offences and the extradition of narcotics offenders

By Dr. Wilhelm Henriehs, Bonn

I

Since the beginning of the century, the international net for catching persons who make wrongful use of narcotic drugs in any manner whatsoever has been drawn steadily tighter. This is the consequence of two developments: the acts constituting unlawful conduct have been defined in more extensive and more precise terms; secondly, steps have been taken to close as far as possible any loopholes in the punishment of offences. So far as substance is concerned, the object was to demarcate the lawful activities concerned with, or the lawful use of, narcotic drugs; so far as procedure was concerned, the object was to enact suitable measures making it possible to proceed effectively against offenders. A further object was that of prevention: by means of appropriate action it was intended, as far as possible, to prevent the occurrence of offences.

The international conventions concerning this subject which have been concluded to date still conform to the classic pattern of international legislation. That is, they bind the States to take certain steps specified in the conventions and to make provision for the punishment of breaches of the law. These conventions do not affect the individual directly.

More recently, the theory has been gaining support among international lawyers that even the individual may have rights and obligations under international law.[1] * Nevertheless, in the discussions on the proposed Single Convention on Narcotic Drugs,[2] which is intended to replace the numerous international agreements by one consolidating instrument, there has been no departure from the traditional position that only States are capable of contracting obligations under international law. This attitude is justified, for the object of the convention is not so much to create something new as to consolidate what is familiar. For practical reasons, too, a case can be made out for this attitude, for it is no doubt easier to persuade the largest possible number of States to participate in an instrument which does not break with tradition. The concept of state sovereignty, which in some circles of the "Old World" is regarded as obsolete and fit for the limbo of history, still exerts a powerful attraction, and especially again nowadays because it is a luminous idea — though it may well be as dangerous for mankind as the naked flame of a candle is for the moths fluttering round it. We should beware, however, of addressing a reproach on this account to the newly independent nations which have but recently entered our community of States that is still cast in the mould of western ideas.

Yet one may venture to predict that the trend of future development will be towards the recognition of direct obligations owed by the individual. Precisely in our field, this development could (as will be explained below) make for considerable progress. The account which follows shows how Germany — to take the example with which the author is most familiar — has participated and continues to participate in the international efforts to combat narcotic drug offences;[3] what domestic measures it has enacted to give effect to the agreements entered into;[4] and what action it can take, consistent with the principles of German international criminal law and with those governing extradition, to close any loopholes in the punishment of drug offences.

II

The International Opium Convention of 23 January 1912 was promulgated in Germany in conformity with article 295, paragraph II, of the Treaty of Versailles.[5] To implement it, the Act of 30 December 1920[6] was passed, article 8 of which contained certain penal provisions. Under these provisions, any persons who, not being thereunto authorized, imported, exported, manufactured, processed, purchased, sold or otherwise dealt in the substances and preparations specified in the Act, or who manufactured, processed, stored, offered for sale or delivered the same in unauthorized places, was liable to imprisonment for a term not exceeding six months and a fine up to 10,000 Marks, or to one of these penalties. Furthermore, a person became liable to penalties if he bought or sold the substances in question without a licence, if he did not respect the quantities or other conditions specified in the licence, if he contravened the export and import regulations, or if he failed to produce satisfactory evidence of his transactions. In addition to imposing these penalties, the court was empowered to order the seizure of the substances involved in the punishable act, regardless of whether these substances were the property of the offender or of a third party.

In passing this Act, Germany went further than it was obliged to do under article 20 of the convention, for under this article, which most scrupulously respected state sovereignty, the contracting powers had merely undertaken to examine the possibility of enacting laws or regulations making it a penal offence to be in illegal possession of raw opium, prepared opium, morphine, cocaine and their respective salts. The question had been duly examined and answered positively, and as a result the statute described was enacted.

The International Opium Convention of 19 February 1925 and the Protocol thereto were ratified by the Act of 26 June

* For footnotes, see pp. 6-7.

1929.[7] Article 28 of this convention set out — and this time in more specific terms — the obligation of the contracting parties to impose adequate penalties, including in appropriate cases the confiscation of the substances and preparations constituting the subject of the offence, for any breaches of the laws and regulations by which the provisions of the convention were enforced. Article 29 provided that the contracting parties would examine in the most favourable spirit the possibility of taking legislative measures to render punishable acts " committed within their jurisdiction for the purpose of procuring or assisting the commission in any place outside their jurisdiction of any act which constitutes an offence against the laws of that place relating to the matters dealt with in the present convention."

As a consequence, the German legislature passed the Act of 10 December 1929 concerning transactions in narcotic drugs, the so-called Opium Act,[8] which is still in force today. Article 10 contains penal provisions under which the offences more particularly specified are punishable by imprisonment for a term not exceeding three years and a fine, or by one of these penalties. As no maximum fine is prescribed, the limit laid down in the general section of the Penal Code[9] applies. The definition of the acts constituting offences is in part identical with that given in the Act of 1920, but some more offences have been added: false representations made to the opium office with a view to obtaining a licence; violation of the ban on the import, transit, export and production of certain substances and preparations more specifically referred to in article 9, and of the ban on dealings in those substances; postal dispatch in violation of the provisions of the conventions of the Universal Postal Union; and certain other offences. In most cases the attempt to commit any of these offences is likewise punishable (art. 10, para. II), as is the commission of any of the offences by negligence, though in the latter case the penalty is less severe (art. 10, para. III). The earlier provisions concerning seizure were supplemented by a clause empowering the court (by proceedings *in rem*, and even in the absence of criminal proceedings) to order the seizure of substances and preparations, in cases where it is not possible to prosecute or sentence a particular person, provided that in other respects the conditions laid down by the statute for the institution of proceedings are fulfilled (art. 10, para. V). This provision is relevant in all those instances in which a narcotic drug is found, but where the importer or owner cannot be apprehended or where the offender cannot be punished by reason of his personal status (e.g., because he possesses diplomatic immunity). For a better appreciation of the position, it should be pointed out that, despite its undoubted penal nature, seizure is not primarily regarded as a punishment in Germany (as it is, for instance, in article 28 of the Opium Convention of 1925), but as a security measure. An alien who is sentenced under the aforesaid provisions may be ordered to leave the territory (art. 10, para. VI).[10]

The examination made pursuant to article 29 of the 1925 Convention does not appear to have yielded any positive results; at any rate, the Opium Act makes no provision for the punishment of acts committed in Germany for the purpose of aiding and abetting the commission of drug offences abroad.

No additional penal provisions were necessary as a result of the Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs, of 13 July 1931.[11] On the other hand, the Convention for the Suppression of the Illicit Traffic in Dangerous Drugs, of 26 June 1936, contains some very specific provisions concerning the duty of the States parties to provide for the punishment of narcotic drug offences and, where applicable, to extradite offenders (articles 2 *et seq.*).[12] But Germany did not become a party to this convention, having by that time ceased to be a member of the League of Nations.

Yet, during the war, by the order of the Ministerial Defence Council dated 6 May 1940 concerning the applicability of the criminal law,[13] the Penal Code was supplemented by an important provision in article 4 of that code (the article dealing with the application of German criminal law to aliens). A provision was inserted to the effect that in the case of illicit traffic in narcotic drugs, the German criminal law would apply to punishable acts committed abroad by an alien, regardless of the *lex loci* (art. 4, para. III, subsection 8 of the Penal Code).[14] This is regarded as an expression of the so-called " universality principle ".

The German system appears to leave no loopholes, especially since under article 3 of the code German criminal law " follows " the person of a German national (the so-called " personal principle "); and yet the position is not quite so simple and clear-cut as it seems, as the following remarks will show.

It is provided in article 10, paragraph I, subsection 1, of the Opium Act that a person commits a punishable offence if he imports, exports, etc. the substances and preparations in question without being in possession " of the authorization provided for in article 3 ". It follows that this provision by its very nature can apply only to acts committed in Germany, since there is no German authority competent to grant permission for the exercise of such activities abroad. For the same reason a person cannot be punished in Germany under article 10, paragraph I, subsection 2, for an act which was committed abroad, for the licence (the lack of which constitutes the offence) is obtainable from a German authority only in respect of a transaction in Germany, and consequently the lack of a German licence for a transaction taking place abroad cannot constitute a punishable offence in Germany. Under article 10, paragraph I, subsection 3, it is a punishable offence to make false representations to the German Opium Office with a view to obtaining a licence. Clearly, this act is likewise only punishable in Germany if committed in Germany. Article 10, paragraph I, subsection 4 deals with offences against article 9 of the Act. Article 9 prohibits the import, transit, export and manufacture of prepared opium and certain other narcotic substances and preparations and transactions in these substances. Manifestly, this prohibition — and hence also its effect in criminal law — can apply only to German territory. Hence, in the nature of things, it is impossible to commit abroad an offence against article 10, paragraph I, subsection 4 read in conjunction with article 9 of the Opium Act. This list could be prolonged, and always one would

arrive at the same conclusion; an exception is the case contemplated in article 10, paragraph I, subsection 7, which provides for the punishment of persons who send narcotic substances or preparations through the mail in violation of the conventions of the Universal Postal Union. In this case, reference is made to international instruments which are meant to protect not merely the German Federal Postal Service, but all postal administrations members of the Universal Postal Union, against such activities. An act violating this provision can constitute an offence against German law, whether it is committed in Germany or abroad.

Accordingly, on closer scrutiny one reaches a somewhat depressing conclusion: although for the purpose of determining whether certain acts, whether committed by German or by foreign nationals, constitute narcotics offences, German law is applicable even in cases where the acts were committed abroad and are not punishable under foreign law, there is no substantive rule of German criminal law that can be resorted to for the purpose of determining such punishable acts; in other words, it is precisely the German law which ought to be applied pursuant to article 4, paragraph III, subsection 8, of the Penal Code, that is lacking. In addition, it should be noted that German criminal law does not recognize " crimes by analogy "; [15] hence, it is not possible, for example, to institute a prosecution under article 10 of the Opium Act on the grounds that a transaction in narcotic drugs has taken place abroad without the official document corresponding to the German authorization or licence, or that false representations have been made to a foreign authority which corresponds to the German opium office. The only offence under international criminal law affected by the extension of the applicability of the German Penal Code is that of sending narcotic drugs through the mail in violation of the Conventions of the Universal Postal Union.

III

A German national accused of an offence by the state prosecutor is always tried by the German courts in accordance with German criminal law. According to article 3 of the Penal Code, German criminal law applies to the acts of a German national whether committed in Germany or abroad. An act committed by a German national abroad is not punishable under German criminal law if, in view of the special conditions in the place of its commission, it is not held to be a punishable wrong (art. 3, para. II, of the Penal Code). Accordingly, there is no punishment in such cases. Furthermore, under article 153 (*b*) of the Code of Criminal Procedure, the state prosecutor may waive prosecution in respect of any acts committed by German nationals abroad. The guiding principle in these cases is not, therefore, the principle of the unconditional application of the law (Legalitätsprinzip) — which is the principle regularly observed in other cases — but rather that of the application of the law in the light of the circumstances (Opportunitätsprinzip).

Article 16, paragraph II, of the Basic Law of the Federal Republic of Germany provides that no German national may be extradited to a foreign country.

It follows that a German national who, while in a foreign country, contravenes that country's regulations concerning the illicit traffic in narcotic drugs (other than the illicit dispatch by post), is virtually beyond the reach of the law if after the commission of the act he succeeds in returning to Germany; owing to the absence of any substantive German penal provisions defining and rendering punishable unlawful conduct abroad and because German courts cannot punish him according to foreign law, he is not punished in Germany, nor can he be extradited to a foreign country to stand his trial in a foreign court.

IV

The benefit of the ban on extradition does not extend to aliens (in so far as they are not persons prosecuted on political grounds who have been granted asylum (cf. art. 16, para. II, second sentence, of the Basic Law [16])). While, therefore — despite the express terms of article 4, paragraph III, subsection 8, of the Penal Code, which extended the applicability of German criminal law — aliens cannot, owing to the lack of substantive penal provisions, be punished in Germany for narcotic drug offences committed abroad, they can in principle be extradited to foreign States for prosecution. Accordingly, it becomes necessary at this point to consider the law relating to extradition.[17]

In Germany, extradition is regulated either by specially concluded international agreements or by the Extradition Act of 23 December 1929.[18] The Act is of only subsidiary importance compared with the international agreement.[19] Since, however, it regulates standard conditions, it will be taken as the basis for the discussion which follows.

Under article 1 of the Act, an alien who is being prosecuted or has been convicted by the authority of a foreign State by reason of a punishable act may, upon the request of a competent authority, be extradited to the government of that State for the purpose of the prosecution or of the application of the sentence. As the use of the word " may " shows, extradition is not mandatory; the ruling on the question of extradition has to be given (according to the statute) by the Land high court (Oberlandesgericht) in whose area the person concerned is apprehended or found (art. 8, para. II, 9, of the German Extradition Act). Under article 2, extradition cannot be ordered except in the case of an act which constitutes a crime or offence (Verbrechen or Vergehen) under German law. In other words, it must be a relatively serious act. Under these provisions, narcotic drug offences would be regarded as extraditable, since they are " offences " (Vergehen) under German law. An important qualification is introduced, however, by article 4 of the Act, which provides that an extradition order must not be made if reciprocity is not assured, or if under German law the prosecution or the application of the sentence in respect of the act would be barred by the lapse of time or by a remission of penalties or for some other reason, or if it has been ruled that the act comes within the jurisdiction of the German courts, and a German (judicial) authority has either given judgement against the person

concerned, or else ruled that the trial of the principal issue should not be proceeded with.

In view of article 4, paragraph III, subsection 8, of the Penal Code one might think that precisely the last-named eventuality could be of significance in the matter of extradition for narcotic drug offences. This is not, however, the case, because (as has been explained above) there is no substantive rule of German criminal law providing for the punishment of narcotics offences committed abroad.

The most formidable obstacle in extradition proceedings is the condition that reciprocity must be assured. The principle of reciprocity is very strictly interpreted by the German courts. It is not sufficient that by the *de facto* conduct of other States reciprocity should appear to be observed in the matter of the extradition of offenders; rather, there must be a legally unassailable guarantee of reciprocity. In addition, the weight of judicial opinion favours the view that it is an essential ingredient of reciprocity that the act by reason of which the request for extradition is made should be punishable in both the countries concerned. According to this view, the necessary reciprocity cannot be said to exist if the State to which the request is addressed could not, in the reverse case, ask for similar judicial assistance on the grounds that the particular offence which has led to the request is not punishable under the laws of the State to which the request is addressed. The intention is evidently to discourage the making of an extradition order, even though an offence has in fact been committed, in any case where the statutory definition of the offence and the conditions governing its prosecution do not correspond in every detail.

This restrictive interpretation of the law on the part of the courts is criticized by learned authors.[20] But quite apart from the objections of doctrine, it is not hard to see that, for purely practical reasons, requests for extradition by reason of narcotic drug offences can give rise to very great difficulties. It is the practice of the courts — using a formula similarly employed in the official argument — to examine whether the act in question would, *mutatis mutandis*, be punishable under German criminal law.[21] They regard article 4 of the Extradition Act as a rule of adjective law that supplements the substantive rule in article 2, which stipulates that the act by reason of which extradition is sought must be punishable under German law. A great expert on the subject who, however, disagrees with the courts on this particular point, has suggested that the difficulties could be overcome if the courts, in considering this question, proceeded from the fiction that the foreign State making the request came within the German jurisdiction, and that German law applied to the act prosecuted abroad.[22] Whether this fiction would advance the solution of the particular case under discussion it is not possible to say without closer examination. The provisions of the Opium Act, breaches of which are punishable under article 10, regulate so many points of detail that it would be a great coincidence if the regulations of a foreign State were to agree with them in every single respect. Consequently, only by means of a very liberal comparison of the definitions, and a waiver of the condition of correspondence in every detail, would it be possible to achieve a satisfactory result.

To sum up: although under the German law relating to extradition now in force the extradition of foreign narcotics offenders is not impossible in principle, yet in practice very serious difficulties may crop up in the consideration of requests for extradition, and as a consequence it is conceivable that persons who have in fact broken the law escape the penalty to which they are really liable.

V

The third draft of the proposed Single Convention on Narcotic Drugs[23] deals with the obligations of the States in the matter of criminal law in chapter IX, entitled " Measures against illicit traffickers ".

By article 45, paragraph I, the parties undertake, " subject to their constitutional limitations " (which appears at any rate a milder formula than that used in article 2 of the Convention of 26 June 1936), to adopt such measures as will ensure that certain acts will be treated as punishable offences, and that serious offences will be liable to severe punishment, particularly by imprisonment or other penalties of deprivation of liberty. The following acts are to be treated as punishable offences:

(*a*) Cultivation, production, manufacture, extraction, preparation, possession, offering, offering for sale, distribution, purchase, sale, delivery on any terms whatsoever, brokerage, dispatch in transit, transport, importation and exportation of drugs contrary to the provisions of this convention.

(*b*) International participation in, conspiracy to commit, and attempts to commit any of these acts; and

(*c*) To the extent permitted by domestic law, preparatory acts.

Under article 45, paragraph 2, the parties further undertake " within the framework of their existing legal systems and ctiminal jurisdiction, and subject to their constitutional limitations " (Could any formula be more cautious if one wishes to achieve anything at all? One is tempted to answer " No.") to adopt such measures as will ensure that

(*a*) Each of the offences enumerated in paragraph 1, if committed in different countries, shall be considered as a distinct offence;

(*b*) Foreign convictions for the offences shall be taken into account for the purpose of establishing recidivism;

(*c*) Serious offences committed abroad either by nationals or by foreigners shall be prosecuted by the State in which the offender may be found if otherwise the offender might escape prosecution.

These provisions are supplemented by article 45, paragraph 3, which deals with the law relating to extradition. The offences specified in paragraph 1 are to be deemed to be extraditable offences. It is, however, provided that extradition is to be granted in conformity with the law of the State to which application is made, and that that State has the right to refuse to effect the arrest or grant the extradition of offenders in cases where the competent authorities consider that the offence is not sufficiently serious.

Article 45 of the draft contains two further paragraphs, which are saving clauses. These are intended to facilitate acceptance of the convention, but make it in fact more difficult to combat narcotic drug offences effectively. Paragraph 4 states that the article must not be interpreted as being prejudicial to the attitude of a party towards the general question of the limits of national criminal jurisdiction under international law. And paragraph 5 provides that nothing contained in the article affects the principle that the offences to which it refers shall in each State be defined, prosecuted and punished in conformity with its domestic law. These provisions, in other words, expressly reaffirm that no attempt is made to formulate definitions of offences under international law by international treaty, or to vest competence for the prosecution and punishment of such offences in international authorities and courts.

It is necessary, lastly, to consider article 46 of the draft, which deals with seizure and confiscation. The former is the official act of temporarily securing the substances in question, the latter the official act of vesting their ownership in the State.

According to the draft, any drugs, substances and equipment intended for the commission of any of the offences referred to in the preceding article are liable to seizure and confiscation. This is in no way an unusual provision. It should be observed, however, that under German constitutional law, the confiscation of the *instrumenta sceleris* cannot normally be ordered unless they are the property of the offender or a party to the offence.[24] In this context one would expect to find provisions concerning also the seizure and confiscation of the *producta sceleris*, which are usually mentioned in the same breath in Germany. The draft is silent on this question.

Article 46, paragraph 2, provides for the destruction of certain substances, for the conversion of others into substances not subject to the Convention or for their use by the Government or under governmental control. This provision does not raise any special problems.

VI

It now becomes necessary to consider whether the conclusion of a convention on the lines of the draft calls for new solutions of the international law problems of the German criminal law regarding narcotic drugs.

The purely domestic legislation concerning narcotic drugs, including the penal provisions, probably does not need amendment to any great extent. On the other hand, the provisions of the German international criminal law, with which this study is specially concerned, will have to be amended.

In the first place, it would have to be provided that if a German or a foreign national contravenes abroad a foreign law which was enacted to give effect to the convention, that person will be liable to penalties in Germany if he is found in Germany (cf. art. 45, para. 2 (*c*)). Whether it is possible in practice to give the German courts competence to rule on the question whether foreign regulations have been violated is open to doubt. How are the courts to acquire the necessary knowledge of the relevant regulations, particularly when they are dealing not with the regulations of a neighbouring country, but with those of Asian or African States? Should they rely only on the definition of the offence as given in the foreign legislation, or should they also be guided by that legislation in the matter of the nature and extent of the punishment? The latter is clearly out of the question. A general scale of penalties applicable in Germany for the infringement of foreign regulations would therefore have to be established. How far this would be compatible with the structure of the German legal system is another weighty problem.

For example, different countries may interpret differently the obligations under article 45, paragraph 1; this difference in interpretation is a potential source of complications. Thus, under paragraph 1 (*b*), conspiracy to commit a drug offence, and under paragraph 1 (*c*), preparatory acts, are to be punishable, but the latter only to the extent permitted by domestic law. What is the difference between conspiracy and preparatory acts? The logical sequence is: conspiracy, preparation, execution. The convention, however, appears to visualize a different order, since the penal provision relating to preparatory acts is qualified, whereas that relating to conspiracy is unqualified. Furthermore, what exactly is the significance of the proviso in paragraph 1 (*c*) " to the extent permitted by domestic law "? It seems merely to repeat the proviso at the beginning of the paragraph, " subject to their constitutional limitations ". Perhaps the difference between the two provisos is that paragraph 1 (*c*) does not mean the words " to the extenet permitted by domestic law " to be construed in a strict sense, based on the hierarchical classification of the sources of the law, but to refer rather to the extent to which the punishment of such acts is standard practice in a particular legal system. According to this interpretation, Germany would not be entering into a commitment by accepting the terms of paragraph 1 (*c*), for under German law preparatory acts are only rarely punishable. Actually, *stricto sensu* illicit traffic is in any case but a preparatory act for narcotic drug offences properly so called. Even on the assumption that there is no obligation to make preparatory acts punishable, there still remains the question why there should be an unqualified obligation to punish conspiracy, which, as was said above, is even further removed from the actual offence than are preparatory acts. In Germany, only conspiracy to commit a crime (Verbrechen) is punishable.[25] Perhaps the clause refers, however, to the " master minds " directing or organizing the illicit traffic, for it has been considered an unsatisfactory state of affairs that gang leaders or organizers who remain in the background should frequently escape punishment.[26]

The object in raising the above problems was to illustrate how the contracting parties might interpret their obligations differently. And the reason why this possibility is relevant to this discussion is that, owing to the many possible differences between national legislations, it becomes extremely difficult to prosecute effectively in a particular country offences which have been committed abroad.

All these difficulties could be avoided if the convention itself defined the offences exhaustively, and in that way established a system of definitions that would be uniform in the territories of all the States parties. It is pertinent to refer to the case of breaches of the regulations of the conventions of the Universal Postal Union; such breaches can be prosecuted in all States, precisely and only because the regulations broken are the same everywhere. Similar instances could easily be cited from international criminal law.

Presumably, the term " abroad " in the draft convention does not mean any foreign country, but only those foreign States which are parties to the convention. Against this interpretation it might, however, be objected that the protection of the country of custody and of its population against narcotic drug offenders, which is the purpose of the prosecution, is of such importance as to justify the institution of criminal proceedings not only on behalf of other States parties, but also on behalf of any State which combats the illicit traffic in narcotic drugs by the enactment of suitable regulations, whether within the framework of the convention or not.

The idea underlying article 45, paragraph 2 (*b*), is manifestly that the repetition of an offence of which the person concerned has been previously convicted constitutes, in general, grounds for imposing severer penalties. This is not the case in Germany, however, for in this country recidivism is only in a few quite exceptional cases the subject of special statutory provisions, and these are to the effect that the nature of the offence changes if there has been a previous *ejusdem generis* offence.[27] Moreover, even in these cases, the German courts invariably take the view that foreign convictions can never establish recidivism.[28] It is consequently unlikely that Germany could enter into a commitment of the kind contemplated in this provision of the convention.

It is of course possible to interpret article 45, paragraph 2 (*b*) differently. It may be intended to mean that the courts are to regard a previous conviction of the offender of a like offence as an aggravating circumstance in determining the precise sentence within the scale of penalties imposable under the law. This is, of course, also the practice of the German courts; but in such cases there is no question of the punishment of recidivism.

The proposed provisions concerning extradition do not appear to offer any great problems. They cover practically all the possible eventualities, subject to the proviso that the law of a State to which application for extradition is made is to apply.

VII

In conclusion it may be said that, while the proposed Single Convention on Narcotic Drugs certainly marks an advance, it will still not produce a completely satisfactory system of international criminal law relating to narcotic drugs. It may not even be possible to establish such a system, because, on the one hand, opinion concerning the dangers of narcotic drugs is still by no means uniform,[29] and, on the other, because the incidence of narcotic drug offences varies from country to country. An appeal should be addressed to the solidarity of States, and the ultimate object should be to work out a definition of the acts which constitute illicit traffic in narcotic drugs under international criminal law.

Notes

[1] *Cf.*, for instance, Georg Dahm, *Problematik des Völkerstrafrechts*, Gottingen, 1956, especially pp. 14 *et seq.*; and Arthur Wegner, " Der strafrechtiche Schutz des Völkerrechts ", in *Materialien zur Strafrechtsreform*, vol. 1, " Gutachten der Strafrechtslehrer ", Bonn, 1954, pp. 357 *et seq.*

[2] *Cf.* United Nations Commission on Narcotic Drugs, reports on eleventh session (Geneva, 23 April to 18 May 1956, E/2891, pp. 20 *et seq*); twelfth session (New York, 29 April to 31 May 1957, E/3010/Rev.1, pp. 44 and 45); and thirteenth session (Geneva, 28 April to 30 May 1958, E/3133, pp. 49 *et seq.*). Reports on these sessions by the German observer (Ministerialrat Danner) were published in the *Deutsche Apotheker-Zeitung*, 1956, pp. 659 to 661; 1957, pp. 597 to 600; and 1958, pp. 723 to 727.

[3] *Cf.* the publication *Bekämpfung von Rauschgiftdelikten*, Wiesbaden, 1956, published by the Federal Criminal Investigation Department, Wiesbaden.

[4] A. Linz, *Die deutsche Opiumgezetzgebung*, Berlin-Göttingen, 1948.

[5] *Reichsgesetzblatt* 1921, p. 6.

[6] *Reichsgezetzblatt* 1921, p. 2.

[7] *Reichsgesetzblatt* 1929, part II, p. 407.

[8] *Reichsgesetzblatt* 1929, part I, p. 215.

[9] Art. 27, part II, subsection 1, of the Penal Code: DM 10,000. If the offence was committed with the object of gain — as most of the offences against the narcotics regulations probably are — the fine may, under article 27 of the Penal Code, be increased to DM 100,000. If the moneys received and the gain derived from the offence by the offender are higher than this upper limit, a fine exceeding this limit may be imposed (article 27 c, para. III, of the Penal Code).

[10] This provision became inoperative by virtue of article 11, subsection 4, of the Deportation Act of 23 March 1934 (*Reichsgesetzblatt*, part I, p. 213).

[11] Proclamation of 10 June 1933, *Reichsgesetzblatt*, part II, p. 319.

[12] Text in: *La Documentation Internationale*, Paris, 1936, pp. 90 *et seq.* This is preceded (pp. 89 to 90) by an informative survey of the development of international law in the matter of action to curb the abuse of narcotic drugs.

[13] *Reichsgesetzblatt*, part I, p. 754.

[14] In the draft of the general part of the Penal Code, Bonn, 1958, the corresponding provision appears in article 6, subsection 11.

[15] Hans Welzel, *Das deutsche Strafrecht*, 6th ed., Berlin, 1958, p. 21. For a detailed discussion, see Walter Sax, *Das strafrechtliche Analogieverbot*, Göttingen, 1953.

[16] *Cf. Entscheidungen des Bundesgerichtshofs in Strafsachen*, vol. 3, p. 392; and vol. 8, p. 59. For a detailed discussion, see Heinrich Grützner, " Auslieferungsverbot und Asylrecht " in: Neumann-Nipperdey-Scheuner, *Die Grundrechte*, vol. II, pp. 583 to 604.

[17] *Cf.* in this connexion Heinrich Grützner, " Staatspolitik und Kriminalpolitik im Auslieferungsrecht " in *Zeitschrift für die gesamte Strafrechtswissenschaft*, Berlin, 1956, pp. 501 to 518; and by the same author, " Die Rechtsprechung des Bundesgerichtshofes in Auslieferungssachen " in Goltdammer, *Archiv für Strafrecht* 1957, pp. 373 to 382.

[18] *Reichsgezetzblatt* 1929, part I, p. 239.

[19] Grützner, *op. cit.* (Goltdammer, *Archiv*), p. 373 under I 4.

[20] In addition to Grützner (see note 17), see in particular Hans-Heinrich Jescheck, " Die internationale Rechtshilfe in Strafsachen in Europa " in *Zeitschrift für die gesamte Strafrechtswissenschaft*, Berlin, 1954, pp. 518 to 544, especially pp. 527 to 529.

[21] *Cf.*, for instance, *Entscheidungen des Bundesgerichtshofs in Strafsachen*, vol. 1, p. 222; vol. 7, p. 265.

[22] Grützner, *op. cit.* (Goltdammer, *Archiv*), p. 378.

[23] E/CN.7/AC.3/9 of 11 September 1958.

[24] It is agreeable that article 10, paragraph V, first sentence, of the Opium Act, in so far as it expressly allows confiscation irrespective of ownership, conflicts with article 14 of the Basic Law.

[25] Article 49 a, paragraph II, of the Penal Code.

[26] In this connexion, see S. Langlais, *Internationale Rauschgiftschmuggler*, in the publication cited in note 3, pp. 139 to 168.

[27] Whereas, for example, under article 242 of the Penal Code larceny is an offence (Vergehen), under article 244 of the Penal Code a repetition of larceny constitutes a crime (Verbrechen). A parallel case is that of fraud (article 263 of the Penal Code) and repetition of fraud (article 264 of the Penal Code).

[28] *Entscheidungen des Bundesgerichtshofs in Strafsachen*, vol. 7, p. 265.

[29] In this connexion, see Erich Hesse, *Die Rausch- und Genussgifte*, 2nd ed., Stuttgart, 1953.

Pharmacology and addiction liability of *dl*- and *d*-propoxyphene

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Introduction

Alpha *dl*-1,2-Diphenyl-4-dimethylamino-3-methyl-2-propionoxy-butane hydrochloride, hereafter designated propoxyphene, was synthesized by Pohland & Sullivan (1). There are four stereoisomers, but only the alpha *d* isomer (*d*-propoxyphene) had analgesic activity in animals (2). In equal doses (32.5 or 65 mg), *d*-propoxyphene hydrochloride and codeine phosphate were equally effective in reducing the discomfort of chronically ill patients (3). In another analgesic study, Gruber *et al.* (4) reported that 50 mg of propoxyphene hydrochloride is approximately equivalent to 32.5 mg of codeine phosphate or 325 mg of acetylsalicylic acid. In a cross-over experiment, Cass & Frederick (5) compared a placebo, codeine (32, 65 and 130 mg), and comparable doses of *d*-propoxyphene for relief of pain in 70 ambulatory, chronically ill patients. Although both drugs were readily differentiated from a placebo, it was not possible to distinguish statistically between equivalent doses of codeine and *d*-propoxyphene; however, codeine in doses of 65 and 130 mg was quite consistently superior to comparable doses of *d*-propoxyphene. On the other hand, in the treatment of postpartum pain, Lasagna & De Kornfeld (6) were unable to demonstrate a statistically significant difference between *d*-propoxyphene (32 and 65 mg) and a placebo. Since propoxyphene is related structurally to isomethadone, and since the *d*-isomer (Darvon, Lilly) is being used clinically, it was thought desirable to investigate their pharmacology, and particularly their addiction liabilities in man.

General Methods

The subjects used in these studies were healthy adult white or negro males serving sentences for violation of state or federal narcotic laws, who volunteered for the experiments. *dl*- and *d*-propoxyphene* were administered as the hydrochloride, morphine as the sulfate, and nalorphine (N-allylnormorphine) as the hydrochloride.

The tests employed to evaluate the addiction liability of these drugs included the following procedures: (i) administration of single doses for the detection of morphine-like (euphorogenic) effects; (ii) substitution of these drugs for morphine in patients addicted to morphine, to ascertain their effectiveness in preventing symptoms of abstinence from morphine (substitutions were for 24 hours and 14 days); (iii) "direct addiction", which involves administration of these drugs in progressively increasing doses as tolerated for 18 days, stabilization on maximum dosage attained for an additional 28 to 36 days, and, finally, abrupt withdrawal of the drug to ascertain the presence and degree of physical dependence; and (iv) precipitation of abstinence by administration of 10 mg of nalorphine subcutaneously after 30 to 40 days of chronic intoxication with propoxyphene. Specific details will be described under each experiment.

Part. I. Propoxyphene

(1) *Effect of single oral doses in non-addicted patients*

The compound was administered orally in single doses in forty-one trials to 25 non-tolerant former addicts, the doses ranging between 50 and 1,000 mg. In thirteen trials with doses of less than 600 mg, no definite subjective or objective effects were recorded. With doses of 600 to 800 mg, patients became drowsy, and most of them reported dizziness. None of the patients stated that the effects were similar to those of morphine, until 800 mg were given, when 3 out of 8 subjects described the effects as resembling those of some kind of opiate. Four of the remaining patients were unable to identify the subjective effects, and one described it as being like barbiturates. One patient, who received 1,000 mg, had severe toxic effects (apprehension, nervousness, tremor, moderate pallor, and perspiration), which predominated over sedative effects.

The effects of a single dose of 600 mg on rectal temperature, pulse and respiratory rates, blood pressure, respiratory minute

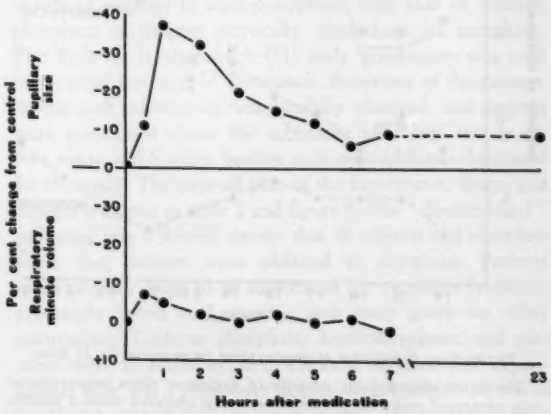

FIGURE 1. — *Average effects (8 subjects) of 800 mg of propoxyphene orally on pupillary diameter and respiratory minute volume*

The average of two pre-drug observations are shown at time zero. The degree of pupillary constriction observed approximates that seen after 20 mg of morphine sulfate given subcutaneously. A single dose of 800 mg of propoxyphene did not significantly depress respiratory minute volume.

* We are indebted to Drs. Brown, Robbins and Gruber, Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Indiana, for supplies of propoxyphene (Lilly 16298) and *d*-propoxyphene (Lilly 21720).

volume, and pupillary diameter were determined in 8 subjects (7, 8). The only significant change in any measurement was a decrease in pupillary size. Figure 1 illustrates observations on respiratory minute volume and miosis.

(2) *Twenty-four-hour substitution of propoxyphene for morphine in patients addicted to morphine*

Eleven subjects who had been stabilized on 240 to 280 mg of morphine daily were given a total dose of 1,200 mg of propoxyphene during the first 24 hours after abrupt withdrawal of morphine. The drug was administered orally in doses of 200 mg at intervals of four hours, except at night, when the interval was six hours. In a similar study, using the same patients, the dose was increased to a total of 2,400 mg, given in divided doses of 400 mg each. In a control experiment, using a comparable schedule, the same subjects were given placebo capsules resembling the propoxyphene capsules. In a positive control experiment, 9 of these 11 subjects were given injections of morphine every four hours, and were informed only that another compound was being tested. The results of this experiment, using the 400-mg dose of propoxyphene (2,400 mg in 24 hours), are illustrated in figure 2. Intensity of abstinence was measured by the hourly point-scoring system (9), beginning at the 14th hour of abstinence, and continuing at hourly intervals through the 24th hour. The t-test for paired observations (10) was used in statistical analysis of data. When morphine was given, the hourly score fluctuated between 3 to 8 points. When placebo injections were substituted for morphine, the intensity of abstinence rose to 32 points at the end of the 24 hours. When propoxyphene was administered in doses of 400 mg every four hours, the intensity of abstinence was significantly reduced, beginning at the 14th hour and continuing through the 24th hour. Two of 9 subjects who received this dosage showed excessive sedation and depressed and periodic respiration, making it necessary to reduce two of the doses to 200 mg for one patient, and one dose for the other patient. Although all the other patients who received this high dosage showed diminished respiratory rate, the depression did not become sufficiently serious to warrant a reduction in dosage. With the 200-mg dose (total 1,200 mg) average intensity of abstinence from the 14th through the 24th hour was as follows: 14, 13, 14, 15, 16, 16 17, 18, 20, 20, and 23 hourly points. These scores are quite similar to those obtained with the 400-mg dose. With the smaller dose, no serious depression of respiration occurred, but definite sedative effects were present.

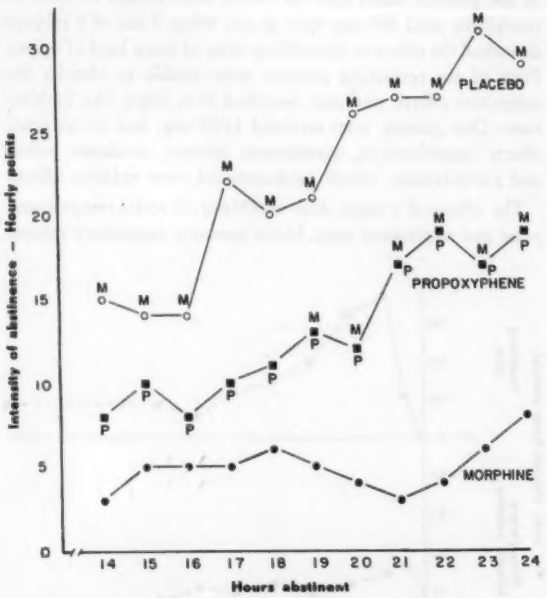

FIGURE 2. — *Substitution of propoxyphene for morphine for 24 hours*

The figure compares the intensity of abstinence when propoxyphene was substituted orally for morphine with that observed when a placebo was substituted, and with that observed when the regular dose of morphine was continued. Each point on the placebo and propoxyphene curves represents the average scores of the same 11 subjects. Each point on the morphine curve represents the average score of 9 of these 11 subjects. The letter P signifies that the point is significantly different from the corresponding point for the placebo; M signifies that the point is significantly different from the corresponding point for morphine, indicating some suppressive effect on abstinence from morphine.

(3) *Direct addiction and precipitation of abstinence with nalorphine*

Five healthy negro males who were former opiate addicts served as subjects. Propoxyphene was administered orally in capsules, and the total daily dose was distributed in three approximately equal doses. The dose was increased as rapidly as practical during the first 18 days of drug administration. Physical dependence was evaluated by abruptly withdrawing

TABLE 1

Drugs and dosages in different periods of the experiment *

Phase of experiment	Days
1. Progressive elevation of dosage of morphine sulfate until a dosage of 280 mg/80 kg per day was attained	18
2. Stabilization on 280 mg/80 kg of morphine	31
3. Substitution of codeine phosphate (1,600 mg/80 kg per day) in 5 subjects, or *d*-propoxyphene (800 mg/80 kg) in 5 subjects	14**
4. Placebo capsules, all 10 subjects	10***
5. Readdiction of all 10 subjects by progressive elevation of dose of morphine sulfate until a dose of 280 mg/80 kg was attained	18
6. Stabilization on 280 mg/80 kg of morphine	31
7. Substitution of codeine phosphate (1,600 mg/80 kg per day) in 5 subjects, or *d*-propoxyphene (800 mg/80 kg) in 5 subjects	14
8. Placebo capsules, all 10 subjects	10
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* Morphine was given subcutaneously in four equal doses daily. Codeine, *d*-propoxyphene, and placebo were administered orally in identical capsules three times daily. The dosage in each capsule was adjusted so that the same number of capsules were given in the case of codeine, *d*-propoxyphene and placebo. The first dose of either codeine or *d*-propoxyphene was administered concurrently with the last dose of morphine at 6 a.m.

** Order of substitution of codeine or *d*-propoxyphene was randomized among patients, and was continued for a variable number of days (13, 14 or 15), so that neither subjects nor observers could anticipate the exact day when the transition to placebo capsules was to be made.

*** On either the 9th or 10th day, all subjects who had continued to take placebos were given instead either one dose of codeine, if they had been receiving codeine; or one dose of *d*-propoxyphene, if they had been receiving *d*-propoxyphene.

propoxyphene after 46 days of addiction, and measuring the intensity of abstinence by the daily point-score system (11). Physical dependence was also measured by administration of 10 mg of nalorphine subcutaneously after 30 to 40 days of addiction, and observing the degree of abstinence induced (12). This procedure was controlled in each subject by the random administration of a placebo instead of nalorphine. Toxicity was evaluated by clinical observations, and by the following laboratory tests which were performed prior to drug administration, and repeated during the fifth and sixth weeks of addiction: routine analyses, red and white blood cell counts, hemoglobin content, hematocrit, and liver-function tests (thymol turbidity and evidence of bilirubin in the urine).

The results of the direct addiction test were as follows: One subject withdrew from the experiment after six days, complaining of nervousness, and that medicine was like LSD (*d*-lysergic acid diethylamide), vomiting and loss of 2.2 kg. Another quit after ten days, complaining that " the medicine makes me nervous; I can't sleep; I'm dizzy, and I'm losing weight " (1.3 kg). In all subjects a maximum dose of 1,200 mg daily was attained. However, it was necessary to reduce this dose to 850, 650 and 700 mg daily in the 3 subjects who continued the test for 46 days. The 3 subjects who completed the test were persuaded to do so by agreement that the dose which provoked significantly disagreeable symptoms would not be given. It should be stated that if a drug induces morphine-like effects, our subjects rarely discontinue a test, and instead of stipulating a minimum dosage to be administered, they request repeatedly that the dosage be increased. Drowsiness was observed repeatedly, and resembled that induced by an opiate, in that they could be readily aroused, but the patients did not consider the subjective effects comparable to morphine-induced " nodding ". Nalorphine (10 mg) precipitated no signs of abstinence, and when propoxyphene was discontinued abruptly, the average scores (11) for the first seven days were 3, 4, 3, 5, 4, 4, and 3. The outstanding observations of the direct addiction experiment were: (i) the compound was disliked by all subjects because of its disagreeable effects (nausea, vomiting, constipation, production of nervousness and dizziness), and because it did not induce morphine-like euphoria; (ii) the compound produced little, if any, physical dependence as shown by the very low abstinence scores after abrupt discontinuation of propoxyphene, and the fact that 10 mg of nalorphine did not provoke signs of abstinence when given after 30 to 40 days of chronic drug administration; and (iii) no evidence of damage to kidneys, liver, or bone marrow was observed in the laboratory tests.

Part II. *d*-propoxyphene

The methods employed and the results obtained in part II (*d*-propoxyphene) were very similar to those presented in part I (propoxyphene). Differences will be pointed out when they occur.

(1) *Effects of single oral doses in non-addicted patients*

The compound was administered as an elixir in doses ranging from 50 to 650 mg. Twenty-three trials were made in 9 subjects. In doses of 50 to 300 mg, effects were minimal, and there was no consistent pattern of response. With doses of 355 to 650 mg, patients liked the subjective effects, and related them to the effects of marihuana, heroin, morphine, and cocaine. With doses of 650 mg, nausea, vomiting and sedation were consistently present, and respiratory minute volume was depressed from 20 to 30% in all patients. Respiratory and pulse rates, rectal temperature, and blood pressure were not affected. (It should be pointed out that a dose of 650 mg is approximately ten times the maximum recommended analgesic dose.)

(2) *Effects of single doses subcutaneously in non-addicted patients*

In five trials, doses of 5 to 60 mg caused no detectable effects. Two subjects given 120 mg reported that they might have received a small dose of morphine, and both complained of soreness at the site of injection. Of 4 subjects given 250 mg, 3 could not identify the effect, and one said it was like a small dose of heroin; 3 showed some miosis; none displayed characteristic morphine-like behavior; and all complained of sore arms.

(3) *Twenty-four-hour substitution of* d-*propoxyphene for morphine in patients addicted to morphine*

Morphine was abruptly withdrawn from 8 subjects who had been stabilized on 240 to 280 mg of morphine daily. At 0, 6, 14 and 20 hours after the last dose of morphine, 200 mg of *d*-propoxyphene were given orally. The intensity of abstinence was reduced significantly, and to the same degree as by propoxyphene (figure 2).

(4) *Comparison of a fourteen-day substitution of* d-*propoxyphene for morphine with that of a fourteen-day substitution of codeine for morphine*

The purpose of this study was to compare the addiction-sustaining capacity of *d*-propoxyphene with that of codeine phosphate in patients physically dependent on morphine. The Kolb & Himmelsbach (11) daily point-score was used to measure intensity of abstinence. Behaviour of the patients during each substitution was carefully observed, and patients were questioned about the subjective effects of the drugs. Five negro and 5 white healthy male post-addicts volunteered for the study. The over-all plan of the experiment, drugs, and dosages is shown in table 2 and figure 3. The " double-blind " technique was followed, except that all subjects and observers knew that patients were addicted to morphine. Patients were told the drugs to be substituted for morphine had been previously tested at Lexington, but were given no other information. Codeine phosphate, *d*-propoxyphene, and placebos were all administered in identical capsules. The experimental plan was a cross-over design — each subject served as his own control for comparing the addiction-sustaining characteristics of codeine and *d*-propoxyphene. Both *d*-propoxyphene and codeine were substituted in a randomized order for 13, 14, or 15 days, then discontinued abruptly, and identical placebo capsules administered. The t-test for paired observations was used in statistical analysis of data (10).

TABLE 2

Daily dose of *d*-propoxyphene substituted for 400 mg of morphine

Subject	Day										
	1	2	3	4	5	6	7	8	9	10	11
L. O.	1 200	1 200	1 200	1 200	1 200	300	300	400	100	200	200
H. A.	1 200	1 200	1 200	1 200	1 100	500	400	400	300	700	500
C. O.	1 200	1 200	900	900	900	900	900	900	600	300	300

Codeine suppressed abstinence from morphine very well, since the average daily point-score after substitution was more than 10 only on the second day (figure 3). When a placebo was substituted for codeine, there was a prompt rise in the intensity of abstinence to an average of 34 points on the third day of substitution, followed by a decline to 20 points by the eighth day (figure 3).

After substitution of *d*-propoxyphene for morphine, the intensity of abstinence rose promptly to 32 points on the second day, but was not as great as would have been anticipated had placebo been given instead of *d*-propoxyphene. This is illustrated by comparison of the intensity of abstinence observed when *d*-propoxyphene was substituted for morphine with that observed in the 65 untreated cases of Himmelsbach (9). Codeine, however, was much more effective than *d*-propoxyphene in substituting for morphine (figure 3). When placebos were substituted for *d*-propoxyphene, there was no significant change in the abstinence scores (figure 3). For comparative purposes, when placebo capsules replaced codeine, there was a prompt and marked rise in the abstinence scores. (It hould be noted that daily abstinence scores, when computed by the method of Kolb & Himmelsbach (11), continued at a relatively high level even after ten days. This is due in part to the persistence of actual symptoms of abstinence, and partly to an artefact in the scores, which arises principally from recovery of respiratory rate and blood pressure to normal levels from the subnormal levels observed during addiction (13). The artefact arises because the baseline

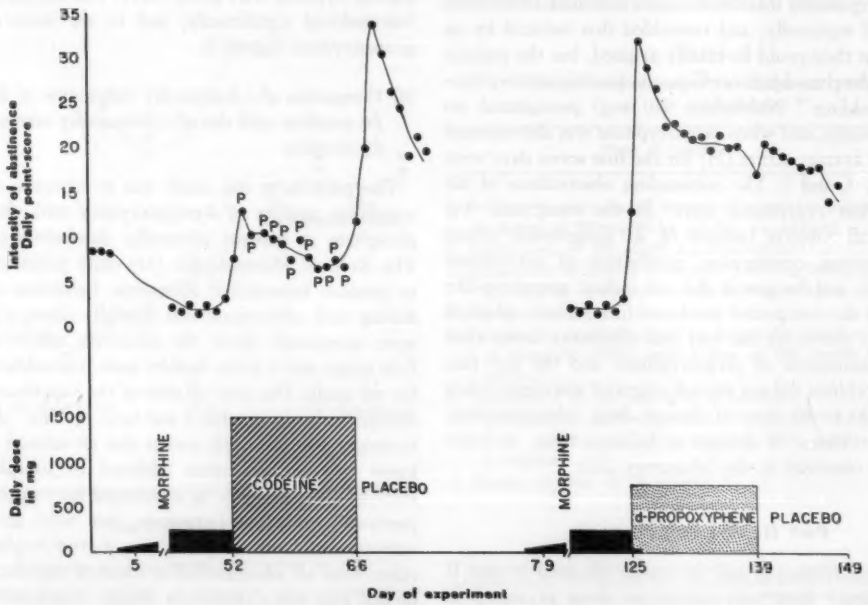

FIGURE 3. — *Substitution of codeine and d-propoxyphene for 10 days*

The figure illustrates (i) the over-all plan of the study and (ii) the intensity of abstinence during various phases, as evidenced by daily point-scores. The data from all 10 subjects have been averaged, and all are represented as having had codeine substituted for morphine first, and subsequently, *d*-propoxyphene substituted for morphine; whereas in the actual design, only 5 of the subjects had this sequence (table 1). The letter P indicates that this point on the curve for substitution of codeine is significantly different from the intensity of abstinence observed at a corresponding point when *d*-propoxyphene was substituted for morphine.

for computing the scores is obtained from observations made during the last 7 to 14 days on the drug, rather than during a drug-free period.)

Patients consistently recognized codeine as a drug in the opiate category, whereas none classified *d*-propoxyphene as an opiate; the majority considered *d*-propoxyphene to be a sedative.

(5) *Toxic psychosis associated with an attempt to completely suppress morphine abstinence by substitution of* d-*propoxyphene in a high dosage*

Morphine was withdrawn abruptly from 3 patients who had been stabilized on 400 mg of morphine sulfate daily, and a high dosage (table 2) of orally administered *d*-propoxyphene was substituted for the morphine for eleven days, after which the propoxyphene was abruptly discontinued. Intensity of abstinence was measured during the eleven days of substitution, and the first seven days after *d*-propoxyphene was discontinued. The average point-scores observed during substitution of this high dosage of *d*-propoxyphene were greater than those observed when 800 mg/kg of *d*-propoxyphene was substituted for 280 mg/kg of morphine.

On the evening of the fifth day that patient L. O. received 1,200 mg of *d*-propoxyphene daily he became extremely agitated, and an emergency call was made for his doctor. He recognized the physician, but approached him on his hands and knees, praying loudly and excitedly. He begged to be taken off medication and discharged from the ward. Interspersed with prayers asking to be forgiven, he recited in a very disconnected way the mistakes of his adult life. He started writing in a frantic manner, and continued in an agitated state all night. Concurrently with the reduction in dosage of *d*-propoxyphene, he improved progressively, and there were no sequelae. Another patient, H. A., was suspected of hallucinating when he was observed peeping out of doors into the corridor, without any particular reason. When questioned the next day, he admitted that at intervals he had been seeing and hearing imaginary people. A third patient, C. O., became nervous and apprehensive, but did not hallucinate, quite possibly because his dosage was reduced to 900 mg on the third day.

In another study using one subject, the intensity of abstinence from morphine was reduced by substituting methadone for a daily dosage of 250 mg of morphine, and then gradually reducing the dosage of methadone. On the third day of this reduction, the patient received 30 mg of methadone and 300 mg of *d*-propoxyphene, and on the fourth day, 20 mg of methadone and 900 mg of *d*-propoxyphene. Abstinence was very satisfactorily suppressed on the fourth day, but that night the patient experienced disturbing hallucinations which promptly receded when the dosage of *d*-propoxyphene was reduced to 300 mg daily.

The above studies, substituting very high dosages of *d*-propoxyphene, were concurrently controlled by substituting only methadone, which was orally administered in a progressively declining dosage to 2 other patients who were addicted to 400 mg of morphine daily. On this regime, abstinence was very effectively suppressed, and no psychotic behaviour developed.

The massive dosages which provoked psychoses in these patients are probably of the order of magnitude which addicts might attempt to use in trying to suppress symptoms of abstinence from opiates. They are from five to ten times greater than the recommended therapeutic doses.

(6) *Direct addiction and precipitation of abstinence with nalorphine*

These were conducted on 5 healthy negro males. In general, the same plan was followed as that described for direct addiction to propoxyphene, except addiction was continued for 53 or 54 days, and laboratory tests were made at weekly intervals.

Dosages of *d*-propoxyphene larger than 800 mg daily may cause severe nausea, marked respiratory depression and even a toxic psychosis. Therefore, dosages significantly greater than this should not be given. This was thought especially advisable, since the degree of tolerance which developed to the toxic effects of the racemic form was much less than that observed for the opiates.

All subjects completed the test. For the first two or three days, all subjects liked the drug, and related the effects to those of morphine, heroin or marihuana, and their behaviour in most respects resembled that of patients given some type of opiate. But subsequently they began to complain — for example, saying: "It doesn't give me the right kind of high," "It makes me too drowsy," or "I'm constipated since starting medication." One patient lost weight slowly but steadily, complained of nausea, and vomited at intervals. It was necessary to reduce his daily dosage from 750 to 600 mg. The other 4 subjects attained a daily dosage of 825 mg, and continued on that level throughout the experiment. At the conclusion of the direct addiction study, the over-all attitude of each subject toward the drug was ascertained: one disliked the effects, 3 were indifferent, and one subject stated, "I think I would go for that medicine; it gives you a relaxed feeling like heroin, but I would rather have heroin." None of the laboratory tests conducted at weekly intervals showed any significant differences from pre-addiction observations.

Following 10 mg of nalorphine, 2 of the 5 subjects showed abstinence signs of slight degree. None of the subjects showed any effects following a placebo injection. (For comparative purposes, it should be stated that if this dose of nalorphine was given to patients addicted to 100 mg or more of morphine for 28 days, a very intense abstinence syndrome would be provoked.)

When *d*-propoxyphene was discontinued after 53 or 54 days of addiction, all of the subjects had subjective complaints (weakness, aching, sensations of heat and cold), and showed objective signs of abstinence, which were largely confined to the mildest category (yawning, lacrimation, rhinorrhea, and perspiration). The average daily point-scores of these 5 subjects during the first seven days of withdrawal of *d*-propoxyphene were 13, 14, 8, 8, and 7 points. By contrast, average scores following withdrawal of codeine in 16 cases reported by Himmelsbach *et al.* (14) for the first five days were much higher (11, 33, 30, 20, and 14 points)

Discussion

These observations indicate by every criterion used — potency in inducing subjective effects resembling those after administration of morphine, ability to suppress symptoms of abstinence from morphine when evaluated in 24-hour an 14-day substitution tests, behaviour during addiction tests, intensity of abstinence following withdrawal, and degree of abstinence precipitated by nalorphine — that the addiction liabilities of both propoxyphene and *d*-propoxyphene are substantially less than that of codeine.

Summary and Conclusions

1. Administration of single doses of propoxyphene (50 to 1000 mg orally) or of *d*-propoxyphene (50 to 650 mg orally or 5 to 60 mg subcutaneously) did not induce a full pattern of morphine-like subjective effects or behavioural changes.

2. Sedation, miosis, depression of respiratory minute volume, nausea, and vomiting were observed with the higher doses of both drugs.

3. When substituted for morphine for 24 hours in addicted patients, both propoxyphene (1,200-2,400 mg orally daily) and *d*-propoxyphene (800 mg daily) partially suppressed symptoms of abstinence from morphine.

4. When substituted for morphine for 14 days, *d*-propoxyphene partially suppressed abstinence, but was much less effective than codeine. Following withdrawal of *d*-propoxyphene, there was no significant change in the intensity of abstinence, whereas after withdrawal of codeine, intensity of abstinence increased very significantly.

5. Attempts to suppress completely abstinence from morphine with high dosages of *d-propoxyphene* (900 to 1,200 mg daily) were associated with a severe toxic psychosis that was readily reversed by a reduction in dosage.

6. Two of 5 patients who received propoxyphene chronically withdrew from the experiment; 3 patients continued after the daily dosage was reduced from 1,200 to 700-850 mg daily; patients disliked the drug because of disagreeable side effects; 10 mg of nalorphine did not precipitate definite abstinence; following withdrawal of propoxyphene, only minimal abstinence was observed.

7. In 5 patients *d*-propoxyphene was administered chronically in high dosage (600-825 mg daily) for 53 days. Early in this experiment, subjective effects and behaviour partially resembling those seen after morphine were observed; these rapidly subsided. After withdrawal of *d*-propoxyphene, only minimal symptoms of abstinence were observed.

8. The addiction liabilities of propoxyphene and *d*-propoxyphene are substantially less than that of codeine.

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Physico-chemical methods for the identification of narcotics (cont.) Part Vb — Paper chromatographic data for narcotics and related compounds

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The Bulletin on Narcotics *presents in this issue the continuation of the Canadian series of articles on the "Physico-Chemical Methods for Identification of Narcotics" which appeared in volumes V (1953), VI (1954), VII (1955) and XI (1959) of this journal.*

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1. Introduction

This study was originally undertaken to develop methods for the rapid qualitative and quantitative separation of morphine, codeine, thebaine, papaverine and narcotine from opium, and has been extended to include both manufactured and synthetic narcotics which are related to the opiates for purposes of cataloguing the routine qualitative and quantitative features for their identification by paper chromatography. A thorough review on paper chromatography of narcotics has previously been given in part Va (7).

2. Materials and methods

The methods were essentially those described in a recent paper by Nadeau et al. (15). A more detailed description of the material, equipment, sources of supply, etc., can be found in United Nations document ST/SOA/SER.K.58, by Farmilo et al. (6).

The results reported in the present paper were obtained by the technique of ascending paper chromatography. Cylindrical jars (12″×18″) and paper cylinders (18″×14″) shaped from Whatman No. 3 MM paper were used. In experiments to determine sensitivity, Whatman No. 1 paper has been employed.

A. Paper Impregnation

Paper impregnated with 0.5 M KH_2PO_4 (pH 4.2) and with $(NH_4)_2SO_4$ (2%, pH 5.3) has been employed.

B. Solvents

Isobutanol: glacial acetic acid: water (100 : 10 : 24) was mixed and shaken until clear. This solution was used as the mobile phase. A small portion of the mobile phase was withdrawn and shaken with water (100 ml) until water-saturated. This aqueous layer was drawn off and used for equilibrating the chromatographic chamber. The isobutanol solvent system was used for most experiments with opium and synthetic narcotics. The times of equilibration and developing were 16 and 18 hours respectively. For the separation of papaverine-narcotine, the following solvent was employed: diethylether (peroxide-free) saturated with 0.1 M acetic acid. Equilibration of the paper required 2 hours, while the development stage required 4 hours. In two dimensional chromatography of opium to separate papaverine and narcotine, development of the chromatogram was carried out with acetic acid (0.1 M) saturated ether along the second dimension, after ordinary development with the isobutanol : acetic acid : water along the first dimension.

C Standard Solutions

Standard alkaloid stock solutions were prepared by dissolving the narcotics (10 mg) in methanol (10 ml) and stored at 4°C. After several days' storage, some solutions became green coloured. Coloured solutions of narcotine when chromatographed show fluorescent bands in addition to those found from freshly prepared solutions. For this reason, solutions of standards were discarded when they became discoloured, and fresh solutions were prepared.

D. Opium Samples

Extracts of opium samples were prepared by triturating opium powder (20/40 sieve size) (0.5 g) with glacial acetic acid (2.2 ml) and water (2.8 ml). The opium triturate was allowed to stand for one-half hour, with occasional stirring, then filtered through a fluted filter paper (Whatman No. 2, 7 cm diameter). This filtrate (5 microlitres) was applied directly to the paper for chromatography.

E. Examination in Ultraviolet Light

After drying at room temperature, the chromatograms were examined under ultraviolet light at two wave lengths, 2537 and 3660 Å. Using Mineralites® and an Aristogrid, cold grid type® ultraviolet source (22″×26″×6″) equipped with filtres.

F. Detection and Identification by Chemical Reagents

Potassium-iodo-platinate was chosen as the spray reagent for detecting and identifying alkaloids on chromatograms. The reagent was prepared as follows: 1 g PtCl 2 HCl. 6 H_2O was dissolved in water (10 ml) and mixed with a solution of KI (10 g) in 250 ml and then diluted with water to 500 ml. Even spraying of the surface area of the chromatogram produces coloured spots varying from blue to violet on a brownish pink background. The colours of the spots of alkaloids differ depending on the kind of salt used to impregnate the paper. The coloured areas were outlined with ball-point ink while the paper was still moist. The centre of greatest colour density of each area was also marked for R_f measurements. Immediate marking of the stained areas was found necessary, since some of the colours fade and shrink rapidly, especially on ammonium sulphate salted papers.

3. Results and discussion

A. Opium Alkaloids and Opium

In table I, a colour code for interpretation of the letters on the chromatogram pictures is given.

TABLE I

Colours of lumineseent areas of chromatograms *

Pure colour	Shade or tint	Other designations
R = Red	Ol = Olive	NC = No well defined colour
O or Or = Orange	Gy = Grey	Weak fluorescence
Y = Yellow	Br = Brown	A = Absorbance
G or Gr = Green	P = Pink	Vl & L = Very light and light
B = Blue	Aqu = Aquamarine	BG^{VL} = Very light blue green
V = Violet		B (Ol) = Blue area with olive zone inside
W = White		

* Code employed for recording results in figures 1 to 6.

It will be observed that the fluorescent patterns of natural opium have characteristic features of colour and intensity which can be described qualitatively, and aid in making comparisons between samples of opium. The first step in characterizing the opium by means of chromatography consists in carefully describing the fluorescent regions according to table I. It will be observed on some illustrations that outlined regions do not have a code letter beside them, indicating that no adequate description of the colour could be given in simple terms. In these instances, the intensity of the colours was described in relative terms as +, ++, +++, etc.

Table II illustrates the limits of detection of the opium alkaloids, morphine, codeine, thebaine, papaverine, narcotine and narceine, using the physical and chemical methods of detection directly on the paper chromatogram. In column 1, the names of the alkaloids are shown, column 2 lists the salt solution with which the paper is treated, including the pH value. Columns 3 to 8 list the lowest concentration of alkaloid in microgrammes (gamma) which were detectable on Whatman 3 MM and No. 1 paper chromatograms using ultraviolet light for the examination. Columns 3 and 4 show the results

TABLE II

Limits of detection of alkaloids in microgrammes

Alkaloid	Salt	UV, mμ						Colour	Spray with K-Iodo platinate		Colour
		3660(t) *		3660(r) *		2537(r)					
		3MM*	1*	3MM	1	3MM	1		3MM	1	
Morphine	M/2KH$_2$PO$_4$, pH 4.2	60	>150	>150	>150	30	30	dark spot $\overset{\bullet}{I}$(A)	5	1	blue
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	60	>150	>150	>150	20	20	on light background	5	2	blue
Codeine	M/2KH$_2$PO$_4$, pH 4.2	>150	>150	>150	>150	20	45		5	3	blue-violet
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	>150	>150	>150	>150	20	45	ditto (A)	5	4	blue-violet
Thebaine	M/2KH$_2$PO$_4$, pH 4.2	>150	150	150	150	2	3		4	4	violet-blue
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	>150	150	150	150	3	10	ditto (A)	5	4	violet-blue
Papaverine	M/2KH$_2$PO$_4$, pH 4.2	1	0.5	1	0.5	0.5	0.5	yellow-green (F)	3	3	violet-blue
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	0.5	0.5	0.5	1	0.5	0.5	spot on darker background	5	3	violet-blue
Narcotine	M/2KH$_2$PO$_4$, pH 4.2	7.5	1	7.5	1	5	1	blue-grey (F)	7.5	5	violet-blue
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	10	3	10	5	10	3	spot on darker background	0.5	0.5	brown-pink**
Narceine	M/2KH$_2$PO$_4$, pH 4.2	>150	>150	>150	>150	30	30	bluish spot (F)	30	30	violet-red
	2% (NH$_4$)$_2$SO$_4$, pH 5.3 ...	>150	>150	>150	>150	30	30	on darker background	7.5	7.5	(Purple) ditto

* t = Transmitted. r = Reflected.

** At concentrations > 30 μg a violet-blue nucleus which is surrounded by the brown-pink area becomes visible.

$\overset{\bullet}{I}$ Probably due to absorption of the ca. 285 mμ maximum by phenanthrene-type compounds indicated by (A) in table. The isoquinoline types fluorescence indicated by (F).

* Whatman number of paper used.

for transmitted light of 3660 Å wavelength through 3 MM and No. 1 paper. In columns 5 and 6, the concentration values detected by means of reflected ultraviolet light of 3660 Å wavelength are shown. In columns 7 and 8, the limits of detection of alkaloids by means of reflected ultraviolet light of 2537 Å wavelength are listed. In column 9, the observed colour or other response of the compound to the ultraviolet radiant energy is shown. In columns 10 and 11, the concentration limits of the drug detected by reaction with potassium iodoplatinate solution sprayed on the paper are shown. In column 12 the colours of the complex formed between the reagent and alkaloids on the paper are given. The background colour of papers salted with phosphate was brownish-pink, and with ammonium sulfate the background colour strikes pink and fades to a mottled grey or white. The fading requires time and was found to be accelerated in daylight. In table III, R_f ranges for five major alkaloids of opium for papers salted with $(NH_4)_2SO_4$ and KH_2PO_4, respectively, are listed. The R_f values were compiled from spots of single compounds, mixtures of compounds and of opium samples covering a concentration range of 2 to 250 γ per spot.

Figure 1 shows a chromatogram of pure alkaloids and opium extracts after iodoplatinate spray. The conditions for this chromatographic experiment were as follows: paper treated with M/2 potassium dihydrogen phosphate, 18" ×24" size, 16 hours' equilibration and 8 hours' developing time. The distance travelled by the solvent front was about 12 inches (30 cm). Isobutanol : glacial acetic acid : H_2O : 10 : 1 : 2.4 was the solvent used for development. The alkaloids were detected by the iodoplatinate reaction, and by ultraviolet light examinations. Below the starting line, the point of application of the alkaloidal solutions indicated by the symbols M= morphine, C = codeine, T= thebaine, P = papaverine, N = narcotine, are shown from left to right. The sixth group of spots on the chromatogram lie above the point where a mixture of these pure alkaloids was applied. Narcotine and papaverine show one spot in the chromatogram. The locations of the fluorescent and stained areas of luminescent constituents and alkaloids of opium are distin-

TABLE III

Alkaloid R_f ranges

Solvent	Iso-BuOH : AcOH : H_2O (10 : 1 : 2.4)			
Paper impregnation....	$(NH_4)_2SO_4$(2%)		KH_2PO_4(0.5 M)	
pH	5.3		4.2	
Alkaloid	Number of spots measured	R_f range	Number of spots measured	R_f range
Morphine	25	0.09–0.14	25	0.20–0.36
Codeine	25	0.17–0.30	25	0.43–0.50
Thebaine	25	0.59–0.70	25	0.69–0.79
Papaverine	25	0.76–0.84	25	0.78–0.87
Narcotine	25	0.76–0.84	25	0.78–0.87

guished by weak pencil lines and heavy ball-point ink lines. Starting at the solvent front and working down the chromatogram toward the origin line, the following fluorescent colours are observed: green (mixture of papaverine and narcotine); area of absorbance (2537 Å), thebaine (only slight concentration); below this is a region of blue-green (BGr) fluorescence in samples 224 D and 803; while sample 711 shows an orange (Or) region. Sample 224 D shows an absorbance followed by a green (G) fluorescence, while none is present in the samples 711 and 803. The next fluorescent region is blue-green. The codeine absorbance spot follows, and is present in all samples 711, 224 D and 803 which are listed in decreasing order of concentration. The next region is an orange or brown fluorescent colour, followed by a heavy absorbance and stained spot which corresponds to morphine. The samples arranged in order of increasing morphine content are 711, 803 and 224 D. All samples show another region of absorbance at about R_f 0.14 which does not stain with the iodoplatinate reagent. The region adjacent to the origin line commonly shows a blue fluorescent zone with a brown centre.

Figures 2 and 3 are photographs of the same chromatogram of pure alkaloids and opiums as follows: sample 711, U.S. customs seizure, No. 63424, originating in Inner Mongolia; sample 224 D, a Turkish druggist opium; sample 803, a sample of chocolate cake opium, probably of Turkish origin. The chromatogram was developed on ammonium sulphate treated paper using isobutanol, acetic acid, water as mobile solvent. Figure 2 is a photograph to illustrate the kind of fluorescent pattern obtained using ultraviolet light (3660 Å). This type of photograph is called a luminogram. Figure 3 is the same chromatogram photographed with visible light after reaction with potassium iodoplatinate reagent. Figure 3 shows that the order of the R_f values is the same regardless of paper treatment with phosphate or sulfate salts. The R_f values are different and depend on the salting technique. The background colour and the colours of the individual spots of alkaloids are different. Figures 4 and 5 illustrate chromatographic comparison of thirteen opium seizure samples. UN 79c* (seizure, El Paso, Texas), U.S. customs seizure 63415, seizure in U.S.A. No. 2, seizure in U.S.A. No. 8, UN 112A,* seizure in Guatemala, seizure in USA 1754, UN 112B* seizure in Guatemala, UN 97* seizure by Mexican Government in Mexico, UN 98* seizure at Linoloa by Mexican Government, Houston seizure in U.S.A., chocolate cake opium seizure in U.S.A. The object of this illustration is to compare the chromatographic appearance of the separated constituents of the seizure No. 1754 with other seizures of apparently similar origin. Figure 4 shows the ultraviolet light picture (luminogram) of the chromatogram treated with potassium iodoplatinate shown in figure 5. Figure 6 is a picture of a two-dimensional chromatogram of an old Indian sample No. 13 from the East Punjab region of India. The paper was saturated with ammonium sulphate and the sample applied in the usual manner. The chromatogram was developed in the second dimension with peroxide-free ether saturated with acetic acid (0.1 N).

Discussion

The object of the study of chromatography of natural opium is to achieve a rapid separation of the major opium alkaloids, morphine, codeine, thebaine, papaverine and narcotine for qualitative and quantitative comparison in the process of determining the origin of opium samples.

Munier & Machebœuf (12, 13) devised the solvent system, isobutanol : acetic acid : water, which is used as the basis of the chromatographic separation of the major opium alkaloids. The system is not quite ideal since papaverine and narcotine are not separated. The separation of papaverine and narcotine was achieved by the method of Krogerus (9). These authors have also shown that the salt with which the chromatographic paper is treated, and the apparent ionic strength of this medium are of importance in the resolution of opium aklaloids. The influence of the ions must be considered, as well as acidity. Resplandy (17) showed that ammonium sulphate when used as mobile phase decreased R_f values more than any other salt investigated. Our preliminary investigations with acetate and McIlvaine buffer confirmed the findings of other workers. In the range between pH 4.0 and 5.0, a higher R_f is generally found with a higher pH (1-5, 10, 11, 16). Comparing the values in table III indicates that the inhibiting effect of ammonium sulphate on R_f appeared to overcome the accelerating effect of increased pH. The ratio of the R_f values of papaverine and morphine may be used as an indication of the spread or resolution obtained with a given solvent system, changing only the salt with which the paper is treated. Using the butanol : acetic acid : water system with sodium acetate, phosphate-citrate, ammonium sulphate and sodium phosphate salted papers the following "spread-ratios" $\left(\frac{R_f \text{ papaverine}}{R_f \text{ morphine}}\right)$ were obtained:

TABLE IV

Spread ratios for opium alkaloids by chromatography on different salt stabilized media

Salt	Acetate	Phosphate citrate	Phosphate	Sulphate
pH	4.19	5.10	4.23	5.35
Ratio	1.48	2.00	2.74	6.66

The ammonium sulphate system has the largest spread between the papaverine, the leading spot on the chromatogram, and morphine, the major trailing spot. Thus, 6.66 is the largest spread ratio and indicates the system in the set, best suited for resolving the largest number of alkaloids.

Reproducibility of R_f values is dependent upon the concentration of the substance whose R_f is being determined. The fluctuations in R_f values for substances from mixtures of pure drugs and raw opium may be seen in table III. The

* This sample is not included in the "List of authenticated samples in the United Nations Distribution Centre" published by the United Nations Division of Narcotic Drugs as document ST/SOA/SER.K/82 (5 January 1959).

concentration ranges vary from about 2 to 250 μg of alkaloid per spot. The change in R_f is also apparently affected by the naturally occurring resins and other material present in opium, which accounts for the apparent spread in R_f values in table III.

One very important feature of paper chromatography is the ease with which mixtures of ultramicro amounts (less than 100 microgrammes) can be resolved quantitatively. The sensitivity of the method for qualitative identification is limited only by the smallest amount that can be detected by physical and chemical tests applied directly to the paper.

The limits of detection, as shown in table II using transmitted ultraviolet light (3660 Å), vary from 0.5 to 150 μg for compounds which fluoresce like the isoquinoline alkaloid, papaverine, and those which absorb ultraviolet radiation like the hydro-phenanthrene alkaloid, codeine. When the wavelength of the light for the detection is closer to the absorption maximum of the phenantherene alkaloids (2850 Å) the limit of detection is improved from 3 to 5 times. Using 2537 Å light, 3 μg of thebaine were detected. It should be observed that the molar extinction coefficient value for thebaine at the maximum is about 5 times that of morphine and codeine, and that the increase in detectability on ammonium sulphate paper is of the same order. In table V some sensitivities of opiates detectable with ultraviolet light and potassium iodoplatinate which were listed in table II are compared with those obtained by Mannering et al (10). These authors used Whatman No. 1 paper sprayed with Sørenson buffer (sodium monohydrogen phosphate mixed with potassium dihydrogen phosphate) and developed the chromatogram with an isoamyl alcohol-acetic-acid-water saturated solvent. A " Menlo Fluoretor " with a maximum transmission of 3250 Å was the ultraviolet source used by Mannering et al. for detection of alkaloids on the paper along with an iodoplatinate spray.

TABLE V

Comparison of observed limits of detection with those obtained by Mannering et al. phosphate-treated papers

Author	Our value	Mannering et al.	Our value	Mannering et al.	Our value
Alkaloid name	Ultraviolet — Wavelength, A			Spray	
	2537	3250	3660	K-iodoplatinate	
Morphine	30	50	150	2	1
Codeine	45	25	150	2	3
Thebaine	3	15	150	2	4
Papaverine	0.5	1	0.5	3	3
Narcotine	1	5	1	5	5
Narceine	30	20	150	35	30

The sensitivities found in this laboratory are in general of the same order as those obtained by Mannering et al. The amount of drug detected using ultraviolet light remains about the same for isoquinoline alkaloids, papaverine and narcotine for all light sources, with the exception of narceine which decreases remarkably in sensitivity as the wavelength shifts from 3250 to 3660 Å. The minimum amounts of alkaloids detected by the chemical reaction on the paper with potassium iodoplatinate by Mannering et al. (10) and by ourselves are quite comparable. Slight differences in sensitivities with which the chromatograms were treated may account for the difference in concentration of the salts. In Mannering's work, the buffer was sprayed on and dried, and in our work the papers were dipped.

Büchi & Schumacher (4), on the other hand, report a lower sensitivity — namely, 10 μg for morphine, codeine, thebaine, papaverine and narcotine. They used the Zaffaroni-modification (19) of the iodoplatinate spray whereas, in Mannering's and our studies, the spray as suggested by Munier & Macheboeuf (12) has been employed.

Samples of opium may be compared with one another by means of paper chromatography. The qualitative comparison of the composition may be carried out, and the approximate quantities of their constituents estimated. The results of experiments with two means of detection and estimation, by ultraviolet light examination, and by spraying with potassium iodoplatinate reagent have been discussed. For opium origin determinations, samples of opium whose similarities of origin have been determined by other physical-chemical methods may be compared on a single sheet. The unknown placed on the centre spot of the origin line is flanked with samples of known origin, and similarities of composition may then be determined chromatographically. Figure 5 shows sample U.S. seizure 1754 to contain 4 major alkaloids in sufficient quantity to produce colours with potassium iodoplatinate. Samples 168, 167 and 162 do not contain 5 major alkaloids as do the other samples. Samples 168, 167, 162, 166 and 172 Florida seizure have approximately similar codeine concentrations. Morphine content of 168, 166 and 172 are also approximately equivalent, while those of 167 and 162 are slightly higher. The thebaine content of 172, 167, 162 and 166 are similar. The thebaine concentration of 168 is highest. Comparing the intensities of the papaverine-narcotine spots, it was observed that 172, 167 and 162 are similar, while the narcotine spot in 166 and 168 are least and most intense respectively. The observations of luminescence colours, and their intensities, have been summarized in table VI. The samples all compare closely in the colours observed, and in

TABLE VI

Comparison of lumineseenee colour patterns of five opium samples on a chromatogram — Figure 5

Luminescence colours	Sample number				
	168	172	167	162	166
Green	Gr	Gr	Gr	Gr	Gr
Brown	Br^L	Br^L	Br^L	Br	Br
Absorbance	A	A	A	A	A
Blue	B^L	B^L	B	B^L	B^L
Yellow	Y^L	—	—	—	—
Blue	B	B	B	B	B
Blue (Brown)	B (Br)	B (Br)	B (Br)	B (Br)	B (Br)
Absorbance	A	A	A	A	A
Brown (Green)	Br (Gr)	Br (Gr)	Br (Gr)	—	Br (Gr)
Blue (Brown)	B (Br)	B^L (Br)	B^L (Br)	B^{VL}	B^{VL}

their intensities. Samples 172 and 167 are very similar. The approximate quantities of opiates present in nine samples, considered to be of similar origin, were compared and summarized in table VII.

TABLE VII

Comparison of alkaloids present in the nine opium samples shown in figure 5

Alkaloid name	Sample number and approximate quantity of opiate								
	165	171	824	830	168	172	167	162	166
Papaverine/ narcotine	5+	1+	4+	3+	6+	3+	3+	2+	1+
Thebaine	1+	3+	3+	3+	2+	2+	2+	1+	1+
Unknown	2+	2+	3+	3+	0+	0+	0′	0	1+
Codeine	1+	1+	6+	2+	4+	3+	3+	2+	3+
Morphine	1+	1+	6+	4+	2+	2+	3+	3+	2+

The conclusion from a comparison of the luminescence pattern and approximate relative alkaloidal composition is that samples 167 and 172 are practically identical, and closely similar to 168 and 162.

B. Manufactured and Synthetic Narcotics

A second objective of the chromatographic study was to compare the R_f values of substances related chemically and physiologically to those of the opiates. Paper chromatographic studies of manufactured and synthetic narcotics can be found in our review of the literature (7). The paper chromatographic behaviour of most of the narcotics, under international control, and of related compounds which may be found in connexion with narcotics, were studied and catalogued with the chromatographic systems described in section 2 of this article.

Tables VIII and IX give a survey of these results obtained in the Iso-BuOH : AcOH : H_2O system on paper salted with phosphate and sulphate. The name of the compounds accompanied by (N) designates a narcotic under international control. The international non-proprietary names were used throughout wherever applicable. The paper chromatographic properties of a compound were characterized by the R_f values shown in column 3, tables VIII and IX.* R_x values (R_f relative to a standard compound) have been used in the narcotics field by Goldbaum (8) and Nadeau (14) (codeine = R_{COD}), and by Thomas & Roland (18) (morphine = R_{MOR}). The R_{COD} and R_{MOR} values are given in columns 4 and 5, respectively. Further characterization of a compound has been obtained by noting the colour of the stained spot after the potassium iodoplatinate spray (column 6), and by examining the chromatogram prior to spraying under the ultraviolet light of 2537 Å and 3660 Å (columns 7 and 8). The R_f, R_{MOR} and R_{COD} values represent averages of 8 or 10 spots obtained from 4 or 5 different chromatograms. Fifty microgrammes of each compound have been used for each spot. The reproducibility of the R_f values was ± 0.02.

Tables VIII and IX illustrate the possibility of separating narcotics and related compounds of widely different chemical structure but similar pharmacological properties. The compounds are arranged according to increasing R_f value.

* Tables VIII and IX may be found on pp. 22 and 23.

4. Conclusions

A method for the chromatographic examination of opium and its alkaloids and related compounds has been devised. The method, including reagents, materials, chemicals and equipment for the procedure, has been described. Typical patterns obtained on chromatographing the pure alkaloids and opium samples have been shown, and the main factors controlling the R_f values have been investigated. R_f values for the major alkaloids of opium under different conditions of development, paper treatment, etc., have been reported. The effect of ion composition and pH of the supporting paper has been tabulated. R_f values for 64 narcotics and related compounds in two different media have been listed. The limits of detection of the major alkaloids of opium have been investigated, and the minimum quantities (microgrammes) detected by physical and chemical means have been discussed. The method for obtaining the approximate alkaloidal composition of a number of opiums has been discussed in relation to an opium origin determination.

5. Acknowledgements

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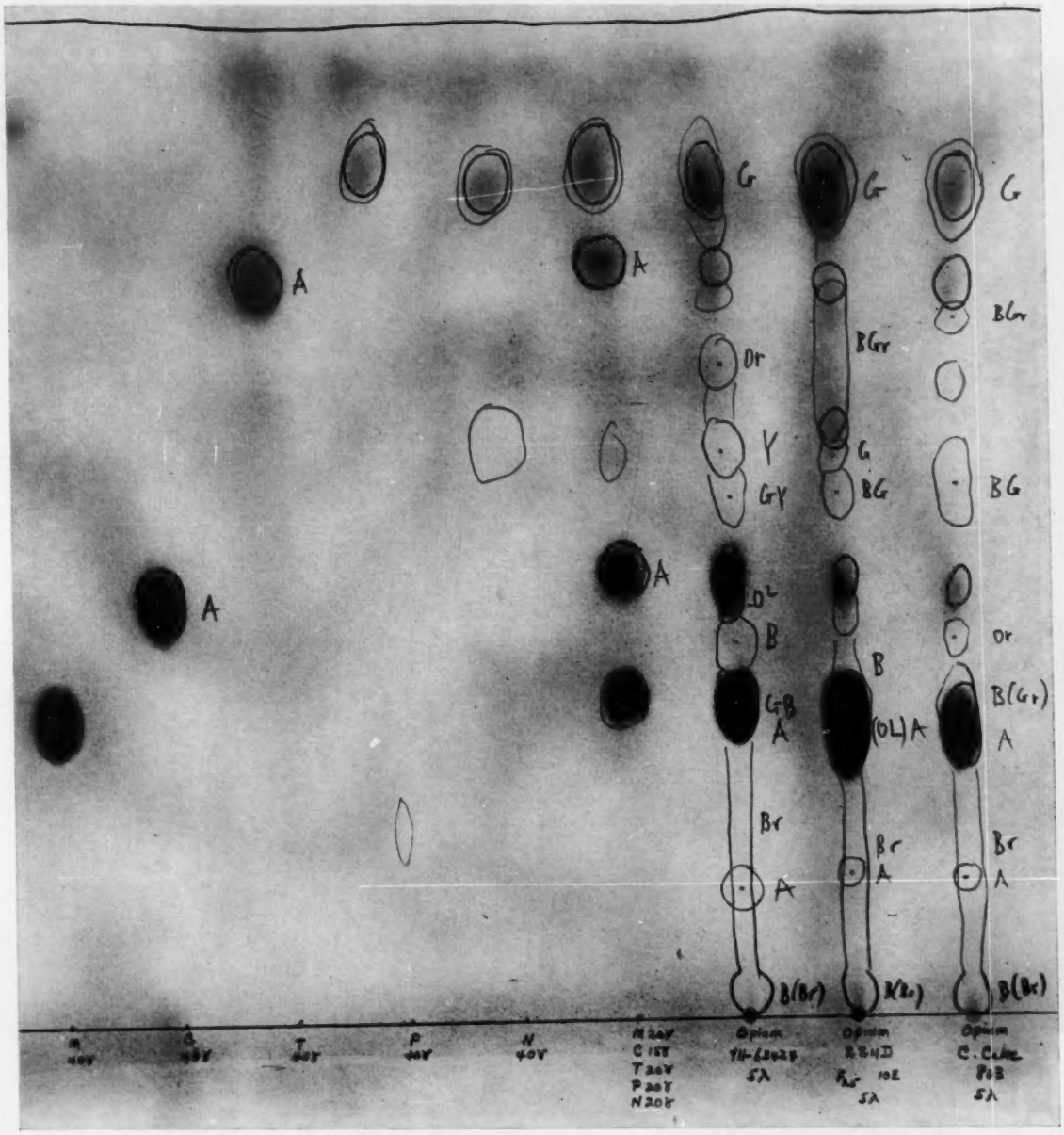


FIGURE 1. CHROMATOGRAM OF PURE ALKALOIDS AND OPIUM EXTRACTS AFTER K-IODOPLATINATE SPRAY

Figure 1. CHROMATOGRAMME D'ALCALOÏDES PURS ET D'EXTRAITS D'OPIUM APRÈS PULVÉRISATION D'IODOPLATINATE DE POTASSIUM

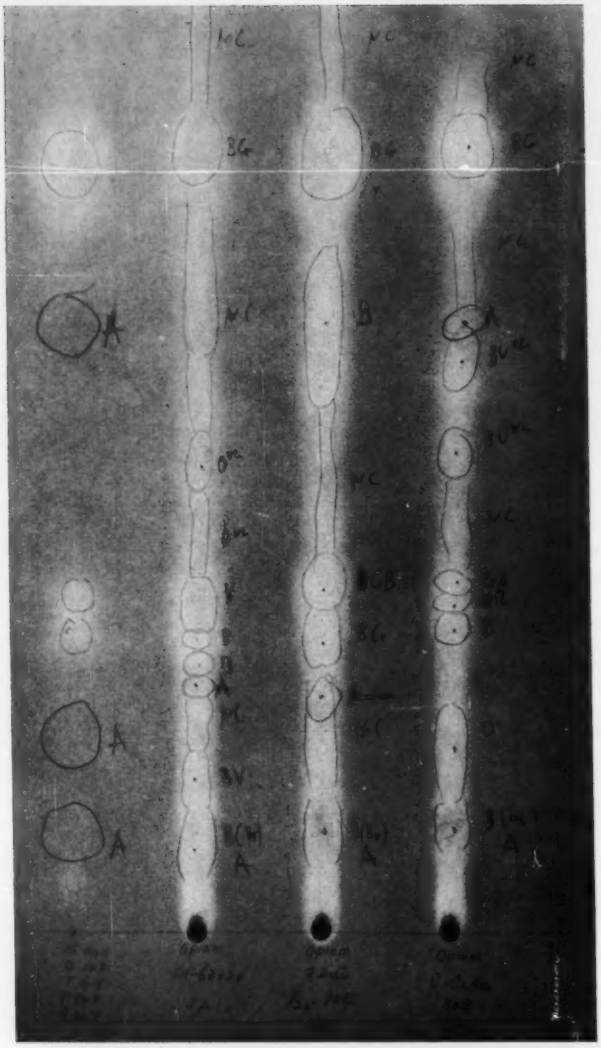


FIGURE 2. CHROMATOGRAM OF PURE ALKALOIDS AND OPIUM EXTRACTS WITH TRANSMITTED UV LIGHT

Figure 2. CHROMATOGRAMME D'ALCALOÏDES PURS ET D'EXTRAITS D'OPIUM EN LUMIÈRE ULTRAVIOLETTE TRANSMISE

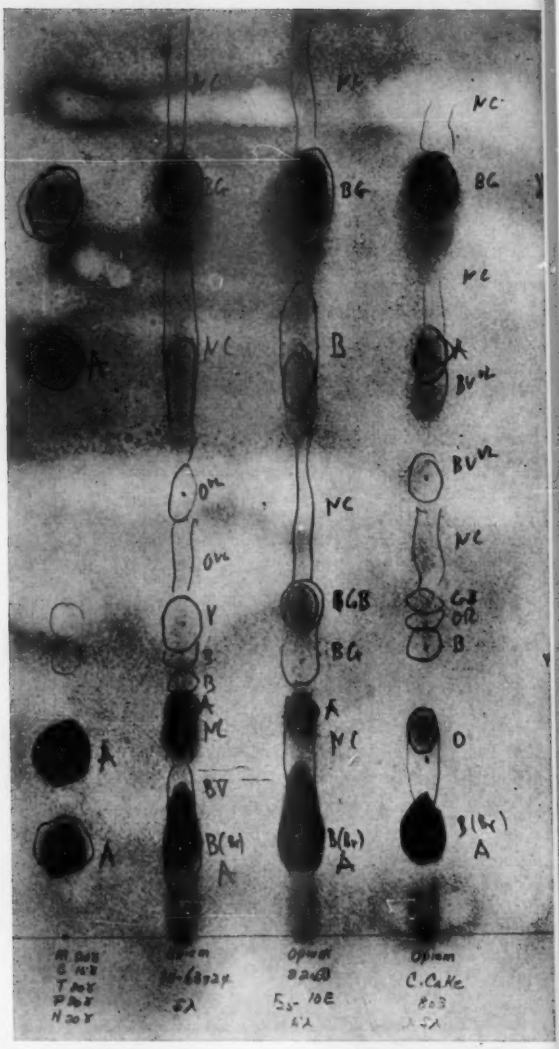
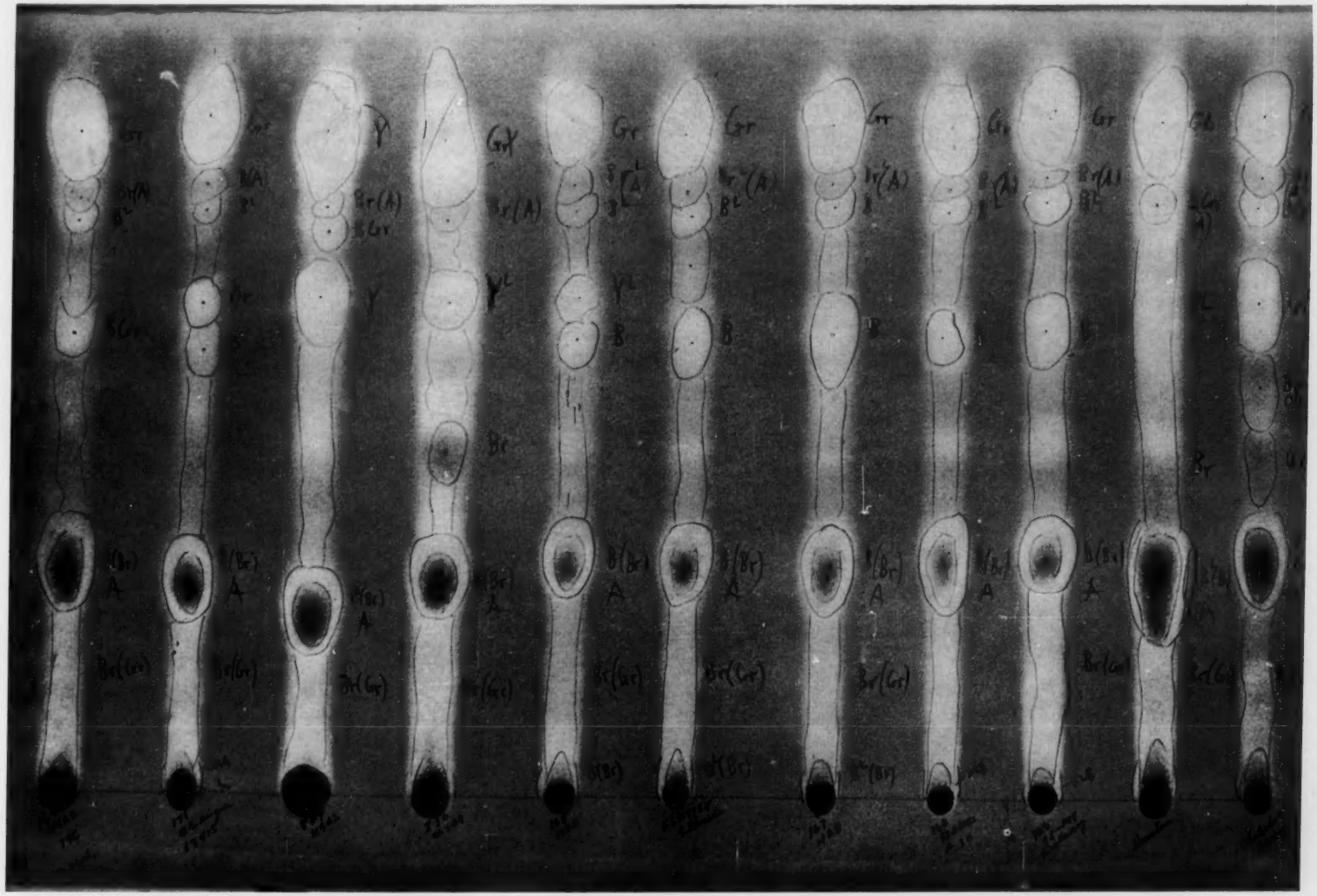


FIGURE 3. CHROMATOGRAM OF PURE ALKALOIDS AND OPIUM-SPRAYED WITH K-IODOPLATINATE

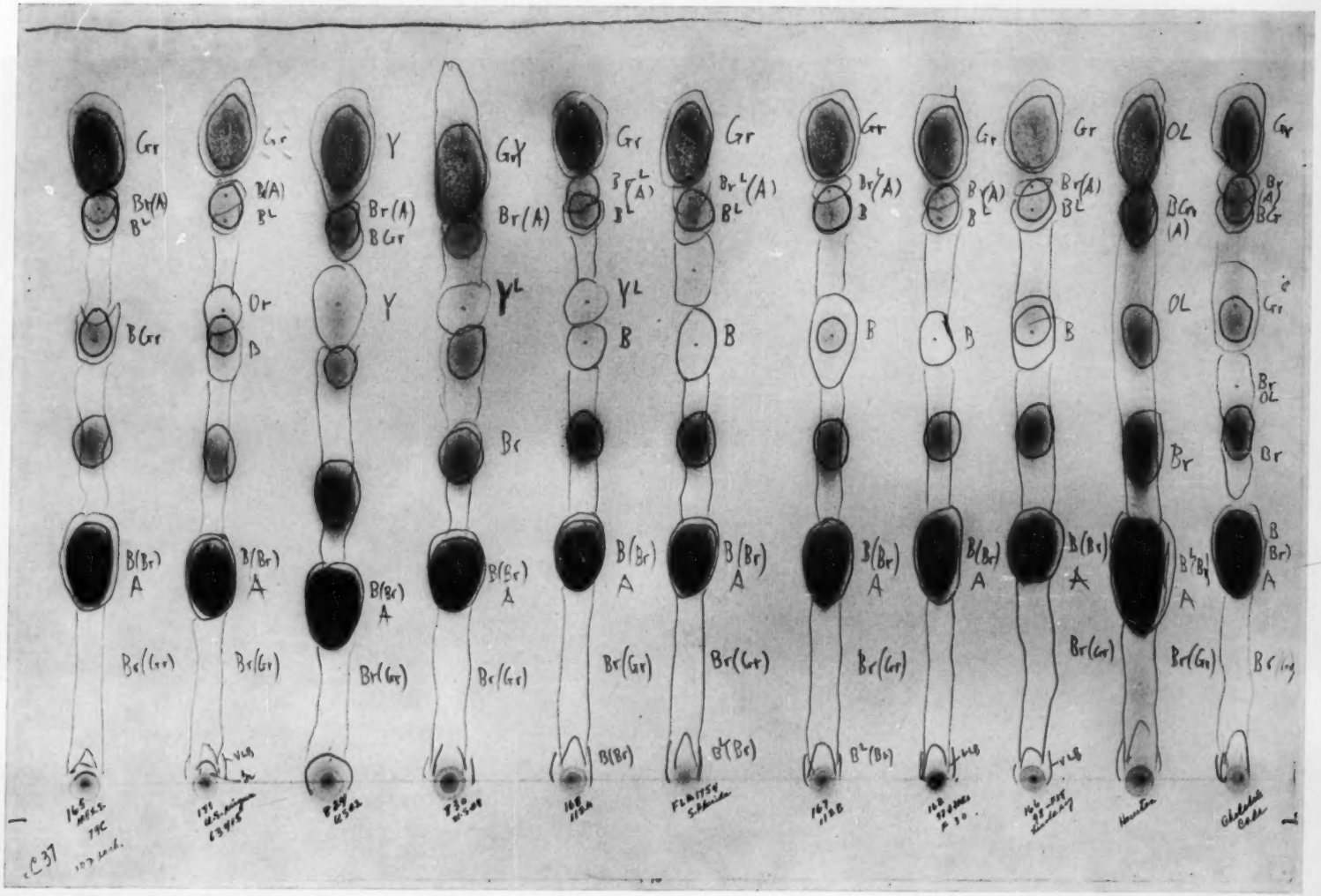
Figure 3. CHROMATOGRAMME D'ALCALOÏDES PURS ET D'EXTRAITS D'OPIUM, APRÈS PULVÉRISATION D'IODOPLATINATE DE POTASSIUM



165 171 824 830 168 172 167 162 166

Figure 4. CHROMATOGRAM OF OPIUM SAMPLES OF DIFFERENT ORIGINS UNDER TRANSMITTED UV LIGHT

Figure 4. CHROMATOGRAMME D'ÉCHANTILLONS D'OPIUM D'ORIGINES DIVERSES EN LUMIÈRE ULTRAVIOLETTE TRANSMISE



165 171 834 830 168 172 167 162 166

Figure 5. Chromatogram of opium samples from various sources (origin). Same as fig. 4, but after K-iodoplatinate spray

Figure 5. Chromatogramme d'échantillons d'opium d'origines diverses effectué dans les mêmes conditions qu'a la figure 4, mais après pulvérisations d'iodoplatinate de potassium

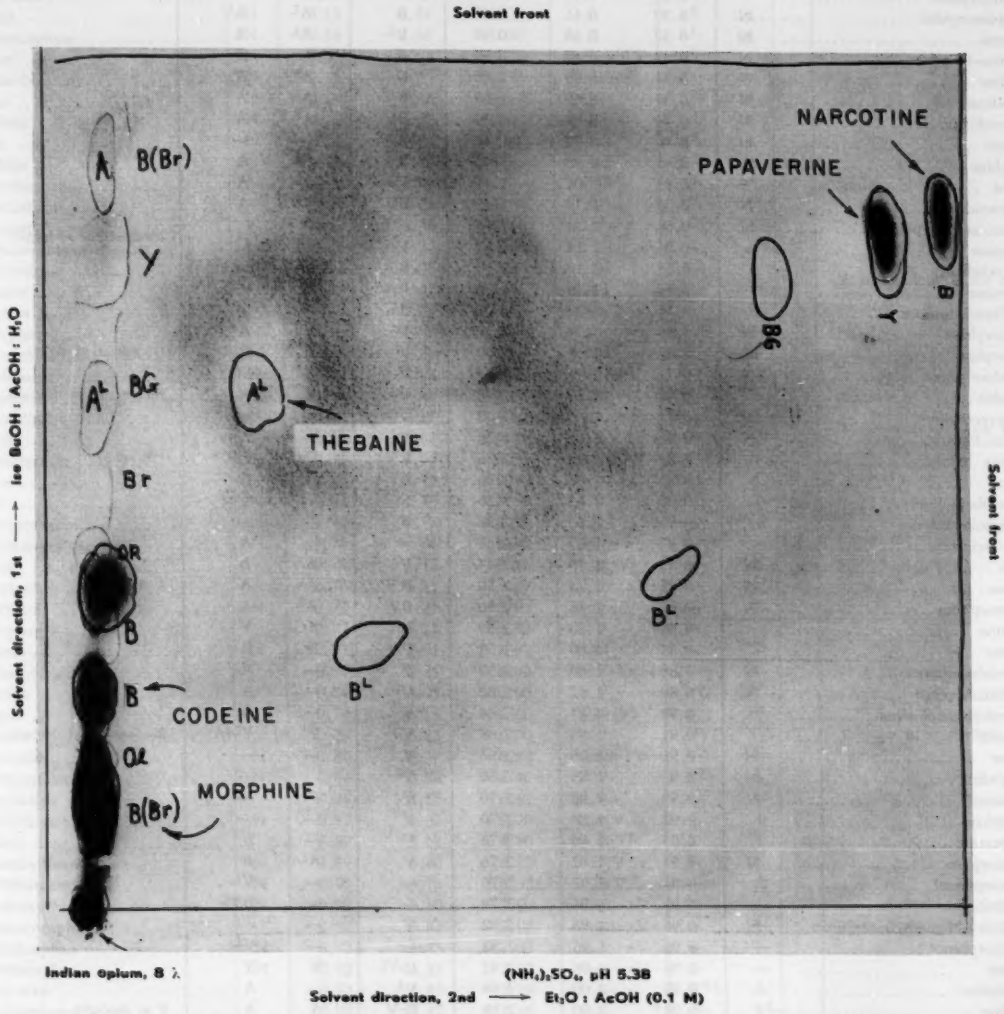


Figure 6. TWO-DIMENSIONAL CHROMATOGRAM OF EAST PUNJAB INDIAN OPIUM

TABLE VIII. — **Paper chromatographic data of narcotics and related compounds**
Solvent: Iso-BuOH : AcOH : H_2O (10 : 1 : 2.4) — Paper: Whatman No. 3 MM, salted with 0.5 M KH_2PO_4

Name of compound	N*	R_f	R codeine	R morphine	Colour with K-iodo-platinate	Observations with transmitted ultraviolet light, Å wavelength		Remarks
						3660	2537	
Meconic acid		0.04	0.08	0.18	—	B	B	
Pholcodine	N	0.08	0.16	0.24	V	—	A	
Pseudomorphine		0.09	0.18	0.26	V	—	B	
Dihydromorphine	N	0.30	0.61	0.88	B	A^L	A^L	
Thebacon	N	0.32	0.65	0.94	V^L	A^L	A	
Morphine-N-oxide	N	0.33	0.67	0.97	—	A	A	
Morphine	N	0.34	0.69	1.00	B	A^{VL}	A	
Oxycodone	N	0.34	0.69	1.00	V^L	A^L	A	
Hydrocodone	N	0.46	0.94	1.30	BV	A^L	A	
Metopon	N	0.46	0.94	1.40	B	—	—	
Nalorphine		0.48	0.98	1.40	BV	A^L	A	
Codeine	N	0.49	1 00	1.40	BV	A^L	A	
Dihydrocodeine	N	0.56	1.14	1.65	BV	A^L	A	
α-Monoacetylmorphine	N	0.56	1.14	1.65				
Cryptopine		0.56	1.14	1.65	V	Ol	O	Fluorescence at higher R_f than stain
Morphothebaine		0.58	1.18	1.70	V	V^L	$B(A^L)$	
Sinomenine		0.58	1.18	1.70	V	A	A	
Methylketobemidone		0.65	1.32	1.91	BV	—	A	
Ethylmorphine	N	0.66	1.34	1.94	V	A^L	A	
Apomorphine		0.68	1.39	2.00	V →B	A	BG	Grey-B at daylight
Diacetylmorphine	N	0.73	1.49	2.14	V	—	—	
Thebenine		0.78	1.59	2.14	V	A	A	Becomes Br at daylight
Hydroxypethidine	N	0.79	1.61	2.32	V	—	—	
Ketobemidone	N	0.80	1.63	2.35	V	—	A^L	
Cotarnine		0.80	1.63	2.36	RV	Or[a]	OR[a]	[a](R =0.5)
Narceine		0.80	1.63	2.36	BV	A^L	A	
Acetoketobemidone		0.80	1.63	2.36	V	—	—	
Propylketobemidone		0.81	1.65	2.38	V	—	—	
Opianic acid		0.82	1.67	2.41	—	—	A	
Cocaine	N	0.83	1.70	2.44	V	A	A	
Thebaine	N	0.85	1.73	2.50	RV	A^L	A	
Hydromorphone	N	0.87	1.78	2 56	BV	A^L	A	
Papaverine		0.88	1.80	2.59	V	YG	Y	
Narcotine		0.88	1.80	2.59	V	BG	B	
Dimethylthiambutene	N	0.88	1.80	2.59	V	—	A	
Diethylthiambutene	N	0.89	1.82	2.62	V	—	A	
Ethylmethylthiambutene	N	0.90	1.84	2.64	V	—	A	
Codeinone		0.91	1.85	2.68	V	Y^L(A)	Y^L(A)	Becomes Br at daylight
Pethidine	N	0.91	1.85	2.68	V	—	—	
Alphaprodine	N	0.91	1.85	2.68	V	—	—	
Levorphanol	N	0.92	1.88	2.70	V	—	—	
Dextrorphan		0.92	1.88	2.70	V	—	—	
Ethoheptazine		0.93	1.90	2.73	V	—	B	
Benzylmorphine	N	0.94	1.92	2.76	V	A^L	A	
Acetylmorphenol		0.94	1.92	2.76	—	—	V^L	
Diacetylmorphol		0.95	1.94	2.79	—	—	BV^L	
l-2-Methoxy-N-methylmorphinan	N	0.96	1.96	2.82	V	—	—	
Methylmorphenol		0.96	1.96	2.82	—	—	V^L	
Dioxyline		0.96	1.96	2.82	Br^{VL}	Y	Y	
Ethylnarceine		0.98	2.00	2.88	V^L	—	A	
Xanthaline		0.98†	2.00	2.88	BrV	A	A	Y at daylight
Racemethorphan	N	0.98	2.00	2.88	BV	—	—	
Dextromethorphan		0.99	2.02	2.91	BV	—	—	
Levomethorphan	N	0.99	2.02	2.91	BV	—	—	
Phenadoxone	N	0.99	2.02	2.91	RV^L	—	—	
Methadone	N	1.00	2.04	2.94	V	—	A^L	
l-Isomethadone	N	1.00	2.04	2.94	V	—	—	
d-Isomethadone	N	1.00	2.04	2.94	V	—	—	
Dipipanone	N	1.00	2.04	2.94	V	—	—	
Alphaacetylmethadol	N	1.00	2.04	2.94	V	—	—	
Alphamethadol	N	1.00	2.04	2.94	V	—	—	
Betaacetylmethadol	N	1.00	2.04	2.94	V	—	—	
Betamethadol	N	1.00	2.04	2.94	V	—	—	
Ethylpethidine		1.00	2.04	2.94	V	—	—	

N* = Internationally controlled narcotic.

† Tailing.

TABLE IX. — **Paper chromatographic data of narcotics and related compounds**
Solvent: Iso-BuOH : AcOH : H_2O (10 : 1 : 2.4) — Paper: Whatman No. 3 MM, salted with $(NH_4)_2SO_4$ (2%)

Name of compound	N*	R_f	^{R} codeine	^{R} morphine	Colour with K-iodo-platinate	Observations with transmitted ultraviolet light, Å wavelength		Remarks
						3660	2537	
Pholcodine	N	0.03	0.13	0.23	BV	—	—	
Pseudomorphine		0.03	0.13	0.23	BV	—	B	
Meconic acid		0.10	0.42	0.77	—	B	B	
Morphine	N	0.13	0.54	1.00	B	A^L	A	
Dihydromorphine	N	0.14	0.58	1.08	B	A^L	A	
Thebacon	N	0.16	0.67	1.23	Br V→RV	A^L	A	
Morphine-N-oxide	N	0.18	0.75	1.38	P (fading)	A^L	A	
Metopon	N	0.20	0.83	1.54	V	A^L	A	
Oxycodone	N	0.22	0.92	1.69	V^L	A^L	A	
Codeine	N	0.24	1.00	1.85	BV	A^L	A	
Nalorphine		0.24	1.00	1.85	VB	A^L	A	
Hydrocodone	N	0.26	1.08		BV	A^L	A	
Morphothebaine		0.32 ††	1.33	2.46	V	V^L	B(A^L)	
α-Monoacetylmorphine	N	0.32	1.33	2.46	V	—	A^L	
Methylketobemidone		0.33	1.37	2.54	V	—	A^L	
Dihydrocodeine	N	0.33	1.37	2.54	BV	A^L	A	
Cryptopine		0.34	1.42	2.61	V	Ol	O	Fluorescence at higher R_f than stain
Sinomenine		0.40	1.67	3.08	V (Br halo)	A	A	
Apomorphine		0.44	1.83	3.39	V	A	BG	
Ethylmorphine	N	0.45	1.88	3.46	BV	A^L	A	
Diacetylmorphine	N	0.50	2.08	3.85	Aqu→V	—	—	
Thebenine		0.58	2.41	4.47	RV †	V	A^L	Becomes Br at daylight
Ketobemidone	N	0.58	2.41	4.47	Aqu→V	—	A^{VL}	
Cotarnine		0.63	2.62	4.85	RV	Or	Or	Fluorescence at higher R_f than stain
Hydromorphone	N	0.64	2.66	4.92	B(V)→V	A^L	A	
Thebaine	N	0.67	2.79	5.16	V	A^L	A	
Cocaine	N	0.67	2.79	5.16	V	A^L	A	
Hydroxypethidine	N	0.70	2.92	5.38	V	—	—	
Acetoketobemidone		0.71	2.96	5.46	Aqu→V	—	—	
Narceine		0.75	3.12	5.77	Br(V)	A^L	A	
Ethoheptazine		0.76	3.17	5.85	V	—	—	
Levorphanol	N	0.77	3.21	5.92	V	—	—	
Dextrorphan		0.77	3.21	5.92	V	—	—	
Pethidine	N	0.77	3.21	5.92	V	—	—	
Propylketobemidone		0.77	3.21	5.92	V (W halo)	—	—	
Papaverine		0.78	3.25	6.00	V	YG	YG	
Narcotine		0.78	3.25	6.00	PBr(V)	B	B	
Codeinone		0.78	3.25	6.00	V	GY(V)	GY(A)	Becomes Br at daylight
Alphaprodine	N	0.81	3.37	6.22	Aqu→V	—	—	
Benzylmorphine	N	0.84	3.50	6.46	V	A^L	A	
Ethylpethidine		0.86	3.58	6.61	V^L	—	—	
Dimethylthiambutene	N	0.87	3.62	6.70	RV	—	A	
Dioxyline		0.87	3.62	6.70	Br^{VL}	Y	Y	
Ethylmethylthiambutene	N	0.89	3.70	6.85	RV	—	A	
Diethylthiambutene	N	0.90	3.75	6.92	RV	—	A	
l-2-Methoxy-N-methylmorphinan	N	0.91	3.80	7.00	Aqu→V	—	—	
Dextromethorphan		0.92	3.83	7.07	Aqu→V	—	—	
Levomethorphan	N	0.92	3.83	7.07	Aqu→V	—	—	
Racemethorphan	N	0.92	3.83	7.07	Aqu→V	—	—	
Opianic acid		0.92	3.83	7.08	—	V^{VL}	A	
Acetylmorphenol		0.93	3.87	7.15	—	—	V^L	
Diacetylmorphol		0.94	3.92	7.23	—	—	V^L	
Alphamethadol	N	0.94	3.92	7.23	RV	—	—	
Betamethadol	N	0.94	3.92	7.23	RV	—	—	
Ethylnarceine		0.94	3.92	7.23	V	—	A	
Methadone	N	0.96	4.00	7.38	V	—	—	
d-Isomethadone	N	0.96	4.00	7.38	RV	—	—	
l-Isomethadone	N	0.96	4.00	7.38	RV	—	—	
Xanthaline		0.98 †	4.08	7.55	BrV †	A	A	Y at daylight
Methylmorphenol		0.98	4.08	7.55	—	A^L	A	
Phenadoxone	N	0.98	4.08	7.55	RV(B)→RV	—	—	
Alphaacetylmethadol	N	1.00	4.16	7.70	RV	—	—	
Betaacetylmethadol	N	1.00	4.16	7.70	RV	—	—	
Dipipanone	N	1.00	4.16	7.70	RV	—	—	

N* = Internationally controlled narcotic. † Tailing †† Elongated spot.

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Poppy cultivation in Bulgaria, and the production of opium

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The opium poppy (1, 2) has been known in Europe since prehistoric times (3).* It is widely cultivated as an oil crop in almost all countries (4). It is cultivated for the sake of opium, however, only in Yugoslavia, Bulgaria and the USSR.

Poppy cultivation was brought over to Macedonia by the Turks at the beginning of the nineteenth century. The first experiments in cultivating it were made in Shtip in 1835, with poppy seed brought over by Aphion Karakhisarski, whence the frequently used appellation, " aphion ", for opium. The first experiments were successful, and the Turkish Government initiated a series of measures to encourage the cultivation of this crop. Because of the favourable climatic conditions and the great demand for opium, its cultivation spread so rapidly that at the end of the nineteenth century the poppy was to be found as far as the Danube valley. It must be regarded as positively established that from this period the poppy was widely cultivated for the purpose of obtaining opium in the Blagoevgrad district (*okrug*). According to other accounts, the poppy was first cultivated within the confines of the old Bulgaria in the countryside around Ferdinandovo (now called Mikhailovgrad), in the Plovdiv area, in 1895, by immigrants from Macedonia. According to still other, unverified information, the poppy was first cultivated in Bulgaria in the Kyustendil sub-district (*okolya*) (5). Originally, it was grown in Bulgaria only as an oil crop, except in the Blagoevgrad district, where it was grown primarily for opium.

Botanical Aspects

According to the classification given by Hegi (1906), the cultivated poppy, *Papaver somniferum L.*, belongs to the

* For general background information on opium (history, botany, etc.), see *Bulletin on Narcotics*, vol. V, No. 3 (special issue on the opium poppy, opium and its alkaloids).

Papaveraceae family. The *Papaver somniferum* is sub-divided into six varieties, according to the colouration of its seeds:

1. *Var. album*, with white seeds;
2. *Var. nigrum*, with black seeds;
3. *Var. caesium*, with blue seeds;
4. *Var. roseum*, with red seeds;
5. *Var. griseum*, with grey seeds;
6. *Var. luteum*, with yellow seeds.

The poppy as it is now found in Bulgaria contains, according to A. Popov, all the above-named varieties, but the most commonly occurring forms are those with white seeds, followed by the blue-seed and the grey-seed forms. The other varieties are found only as mixtures.

According to Bazilevskaya's classification, the cultivated or soporific poppy *Papaver somniferum L.* belongs to the Papaveraceae family. The sub-species *turcicum* grows in Bulgaria; this sub-species occurs in the Mediterranean to eastern parts of Asia Minor, and its bordering regions of Macedonia, Palestine and the Transcaucasian republics of the USSR (6).

In Bulgaria, the poppy is an annual herbaceous plant; it has a fusiform main root, with a few lateral branchings in the surface soil. The stem is erect, and under Bulgarian conditions varies in height from 40 to 180 cm, with three to seven, and sometimes more (up to fifteen), branchings, which are sometimes slightly villous, and covered with a waxy bloom, which gives them a bluish-green colour. The leaves are large, entire or slightly serrated, and shot through with blue or grey-green colours. While the lower leaves are broad and spatulate with dentate margins, and are hairy along the midrib on the underside, the stem leaves are obovate, small, dentate-edged, with a cordate base which encloses the stem.

The buds are small, ovate, and twined round two large sepals which fall off when the flower is shaken. Before flowering, the buds droop.

The flowers are medium large, single, with four petals, usually white or violet. Occasionally, poppies with red or pink petals are found; these are usually entire, and only exceptionally have cut margins. There are 150 to 200 stamens, arranged in five circles.

The fruit consists of a large pod with an incomplete septum which has a smooth surface, or is very slightly segmented. The pod is spherical, oval, or conical in shape.

The stigma is a star-shaped flat disc, with 5 to 16 rays. The pod contains 800 to 2,000 seeds.

The seeds are very small, weighing 60 kg to the hectolitre. The most common colour of the seeds is white or grey. Bluish-grey, coffee-coloured or yellow seeds are sometimes found.

The white-flowered variety of poppy gives white seeds, and the blue-flowered variety, which in fact has violet petals, gives grey seeds (7).

Influence of Climate

For normal growth, the poppy requires a certain definite distribution of rain over the course of the year, according to the soil humidity. Moisture is particularly necessary during the vegetation period. In Bulgaria, climatic conditions suitable for the growth of the poppy exist, and can be utilized to greatest effect if the poppy is sown in autumn. In general, there must be an adequate supply of moisture in the surface layer of the soil if the poppy is to germinate. A large quantity of water is also particularly necessary from the first stages of the plant's growth until flowering begins. Conversely, after flowering is over, a dry soil is required for the cultivation of the poppy for opium. Under these circumstances, a high-quality crude opium is obtained, with a high morphine content. While the bud is growing, rain, and also wind, not only do not help, but are even injurious.

The poppy's response to heat also varies in the course of different stages of its growth. During sowing, cool weather is the most favourable — that is, moderate temperatures; otherwise, the plant grows quickly, but does not become well established, and may die during the winter. A sudden warm spell during late spring or autumn, or immediately after spring sowing, causes the plant to grow rapidly, but without establishing itself, because some pods fail to swell, with the result that the opium and seed yield is low. Conversely, high temperatures during the periods of flowering, harvesting the pods and gathering the opium are favourable for the opium and seed yield. Hot winds, however, are particularly unfavourable during these periods.

The poppy requires a temperature of at least 3 to 4°C in order to germinate; the optimum temperature for germination is 10 to 11°C. The young plants prefer a temperature of 4 to 7°C. For these reasons, in open soil, winter frosts are harmful to autumn-sown popies, and this means that the crop must be sown in spring. Once poppies have survived the winter, they are unharmed by late spring frosts.

The intensity of the sun's heat, especially in the flowering period and while the fruit pods are forming, is of major importance for the accumulation of alkaloids in the milky juice. Under the effect of abundant moisture, the poppy sickens, and the seeds grow in the pod during ripening, and risk becoming completely spoiled.

Influence of Soil

The poppy grows well in a not too dense soil which is sufficiently pervious. It does not take up water from the subsoil. When fertilized with well-rotted manure, it will flourish even in comparatively poor soil, although the field must still be well warmed and free from cold, and possess a good soil structure. Soils which form a spring crust are unfavourable, because they hamper not only germination, but also the subsequent growth of the poppy; this causes development to cease, and leads to a low seed and opium yield.

The poppy is exacting as regards the composition of the soil; it grows well, and gives a rich yield in rich, well-manured soil. Compared with rye, for example, it takes up two and a half times more phosphorous, twice as much potassium, and six times as much calcium. The poppy is successfully cultivated in the light, black earth soil in southern and northern Bulgaria,

as well as in the grey mountain and brown mountain soil in the upland regions — that is, in soils where wheat and other cereals grow.

In the cultivation of the poppy, good results depend to a large extent on applying all the correct technical procedures. In the choice of field, apart from the conditions of soil composition and structure mentioned above, the previous crops must also be taken into account. The practice adopted to this end is to sow the poppy in soil which has been well fertilized with well-rotted manure for the previous crop. This prevents the field from becoming congested with weeds, thereby making it possible to prevent the appearance of the weeds in good time.

Under Bulgarian conditions, the poppy is generally sown either after the winter cereals — especially wheat — in the case of autumn sowing, or after a root-crop, in the case of spring sowing.

The poppy requires very well prepared soil. The soil is first deep-ploughed with plough and coulter, after which the surface is levelled. The early deep-ploughing is a particularly important part of this preparation. Through periodic cultivation and harrowing of the surface layer, the soil becomes friable, and at the same time weeds are kept down.

A great many experiments have been described in the literature, which show that the manuring of the poppy crop plays an extremely important part in securing a high yield (8). Surveys based on questionnaires issued to a large number of individual and co-operative farms, and analysis of their opium production have shown that practical experience confirms that fact. In Bulgaria, experiments carried out in the past on individual holdings and at the labour co-operative farms (TKZS) have provided practical evidence that the good results obtained under experimental conditions can be repeated.

Of the mineral fertilizers, nitrogenous and phosphorus fertilizers have a particularly pronounced effect; they are usually applied twice — the phosphorus fertilizers are, for preference, generally applied directly before sowing, and the nitrogenous preferably during the vegetation period.

Another important factor for good opium yield is the selection of the seed for sowing. In Bulgaria, seed is supplied through the responsible state organization. Before the seed is sown, it is cleaned by being steeped for fifteen minutes in 0.25% formaline solution, washed with water, and then left to dry in an airy, shaded place. Dry disinfection is also practised, by dressing with one of the agricultural preparations used for such purposes (0.5 to 1% tilantin-ceresine, or germisan-trakenboitse).

We use spring sowing only as a last resort. Given successful wintering, autumn sowing always ensures a very high seed and opium yield, in comparison with spring sowing.

Under the climatic conditions which exist in Bulgaria, the period suitable for autumn sowing is the time between 20 September and 10 October, depending on the presence of moisture in the soil. Until recently, sowing was done either by scattering the seed broadcast by hand, or else more or less sparsely in rows, in which case the seed was placed in a bottle with a goose quill attached to its stopper. These methods of sowing are steadily being supplanted as our co-operative farms are becoming equipped with up-to-date agricultural machinery, and there is a growing preference for seeders, which can distribute 1 kg of seed per decare (ca. 0.2 acre) to a depth of 1.5 to 2 cm.

According to the findings of the Sadovsk experimental station, where tests were performed during the period 1928-1931, the optimum distance between the rows is 30 cm, with 15 cm between the plants (relative yield, 101.30).

The yield is scarcely affected if the space between the rows is increased to 40 cm and the distance between the plants is kept at 15 cm (relative yield, 100), or if the distances are reduced to 20 and 15 cm (relative yield, 99.2). It is therefore economically useful to work with large distances between the rows when mechanical tillage instruments are used. On the other hand, experiments in increasing the distance between the individual plants within the rows from 20 to 25 cm led to a fall in the yield. But if advanced agricultural techniques ara used, according to the findings of the national experimental stations, the inter-row distance can be increased to 60 or even 75 cm, provided the number of plants per unit of surface is kept the same as before by reducing the distance between the plants in the rows from 15 cm to 7.5 cm.

The poppy seed takes 10 to 12 days to germinate, after which slow growth continues through the weeks preceding the onset of frosts and snow. After successful wintering, early spring hoeing and thinning are especially important if high yields are to be obtained. Still better results are obtained with autumn hoeing and thinning. Even spring-sown poppies require these operations to be carried out as early as possible. The number of hoeings depends on climatic conditions during the year. Generally, 3 to 4 hoeings are necessary; the soil is thereby kept friable, and weeds are kept down. The plants are usually fed at the same time as the hoeing is done.

Plant Enemies

Protective measures must be taken against a number of diseases to which the crop is subject. The most commonly encountered is *pleosporosis* (9), caused by the fungus *Pleospora calvescens*, which attacks the poppy at all stages of its growth. As a rule, irregular brown specks appear first on the leaves, and gradually grow into oblong spots up to 10 cm long, which spread over the rest of the plant.

Peronosporosis (mildew) is caused by the fungus *Peronospora arborescens*. This is particularly widespread during wet years in the hot weather. It can even wipe out the crop.

Bacterial spot is caused by the *Bacterium papavericola*. At first, numerous, almost circular, spots form; these are brown on top, and olive green underneath, and later become dark brown. The disease is carried by the seed. It is rarely encountered.

Bacterial wilt is caused by the *Bacillus (Erwinia) papaveri*. Dark brown to red spots form. The disease is carried by the seed, and is rarely encountered.

Bean aphid (Doralis fabae) is comparatively widespread in Bulgaria (10).

Fig. 1. Examination of poppy capsules before harvesting

The *poppy weevil (Ceutorrhynchus macula alba)* may be up to 5 mm long. It has a light yellow body covered with grey and yellow hairs, and red antennae. It lays its eggs in the seed pod of the poppy. The larvae are covered on the upper side with a great number of small transversal folds. The chrysalis forms in the soil, where it winters.

The *poppy midge (Cecidonia papaveris)* attacks the fruit pods. Its development is similar to that of the poppy weevil.

The poppy pests can be successfully combated by using advanced agricultural techniques, crop rotation, collecting and burning all the plant refuse after the harvest has been gathered, deep-ploughing the field, using healthy seed for the sowing (decontaminating it before sowing), and by burning diseased plants.

Harvesting

The collection of the opium is done in Bulgaria by incising the poppy-heads during the period of what is known as industrial maturity. This occurs about twenty-five days after the flowering of the greater part of the plant is over, at the beginning of June in the plains of southern Bulgaria, and at the end of that month in the more northern and higher parts of the country. When the plant reaches industrial maturity, the poppy capsules gradually change their greenish colour for one with steely-blue tints, and become covered with a light down. With light pressure the inner sides can be felt, while in the uppermost part of the spathe under the pericarp itself, a light coffee-coloured ring appears. On incision of the pericarp, when only the epidermis and the milky ducts are touched, droplets of milky juice separate out on the surface of the walls. The incision is almost invariably made with a special sharp-edged knife, which penetrates 1 to 2 mm deep. About three-quarters of the capsule is incised horizontally, and the operation stops a little below the broadest part of the capsule. In calm weather, the droplets of milky juice form a string of beads like a pearl necklace. Strong winds, and especially rains, prevent normal collection of the opium. The incision is usually begun after midday, and finished before sunset. Early on the following day, immediately after the dew has evaporated, a milky juice exuding from above the capsule has already collected, dried, and from being white (occasionally pink) has become coffee-coloured and hard.

For collecting the opium, a broad, comparatively blunt knife is used. The opium is placed in a special box in the shape of a truncated cone, called a " safa ", which is belted on to the worker's body.

In Bulgaria, the poppy capsules are incised only once, usually with a single-bladed knife.

The opium yield is collected into a single pool, mixed well and made up into little cakes of 200 to 250 g, which are wrapped in poppy leaves and placed in a shady and sheltered spot to dry. The purchasing organizations sometimes accept it in a semi-liquid condition, and process (malax) it into cakes themselves.

The yield of crude opium per decare varies a good deal (from 0.400 to 2.500 kg).

About three weeks later, the seed is collected from the poppy capsules. This is usually done manually (as the poppy seed is exceptionally small, waste occurs if the collecting is done by machinery). The seed yield per decare varies from 60 to 120 kg.

Fig. 2. Incision of poppy capsules. Region of Sandanski (Bulgaria)

Bulgarian opium is known on the world market for its high content of morphine (11). Our regular five-yearly surveys of the opium yield for the whole country show that Bulgarian opium is high on the world list in respect of quality.

TABLE 1

Morphine content of opiums produced in different countries

Producing country	Percentage of morphine in crude opium
Yugoslavia	13–16
Turkey	12–14
Iran	10
Afghanistan	10–16
India	7.5–10
China	6–8
Mexico	3–6

Bulgaria was not included in the above table. The figures for the percentage of morphine content of Bulgarian opium, according to our own researches, are given in table 2.

The tests were made on average samples taken from export lots of crude malaxed opium throughout the years indicated (13).

As regards opium yield, poppy cultivation in Bulgaria was until recently concentrated almost exclusively in the south-western part of the country.

These regions were not in a position to satisfy the growing requirements of our export trade and our pharmaceutical industry. It therefore became necessary to decide which regions were suitable for developing the cultivation of the poppy or opium so that the over-all area sown to poppy could be extended.

TABLE 2

Percentage of morphine content of Bulgarian opium

Year	Percentage of morphine with 15% moisture	Percentage of morphine with 10% moisture
1949	14.40	15.24
1952	15.58	16.50
1950	16.40	17.35
1948	16.41	17.38
1951	16.45	17.42

For five years (1948-1952 inclusive) we carried out regular research on opium samples taken from every part of the country, both from the old southern regions, and from the new northern regions where, on our advice, poppy sowing had been started. We took average samples from the whole quantity of opium obtained from a given locality, district or region.

For this purpose, the whole quantity of opium gathered from the given locality was thoroughly mixed when the opium was not very hard, and from each part of the general mixture a known equal quantity of opium was taken, which was then mixed on thick glass with a metal spatula until it became completely uniform. The entire quantity was then spread on the glass in an even layer, and proportional quantities

TABLE 3

Content of morphine in crude and anhydrous opium, by years and districts, for the whole of Bulgaria

(In percentages)

Year		1948			1949			1950			1951			1952		
District	Season	Morphine in crude opium	Moisture	Morphine in dried substance	Morphine in crude opium	Moisture	Morphine in dried substance	Morphine in crude opium	Moisture	Morphine in dried substance	Morphine in crude opium	Moisture	Morphine in dried substance	Morphine in crude opium	Moisture	Morphine in dried substance
Petrich	Autumn	11.80	35.54	18.40	—	—	—	12.34	34.50	18.84	12.03	37.50	19.10	10.97	34.74	16.81
	Spring	—	—	—	12.91	23.10	16.79	—	—	—	—	—	—	—	—	—
Sandanski	Autumn	12.70	32.06	18.69	—	—	—	12.34	34.50	18.84	12.12	35.36	18.71	11.98	32.84	17.81
	Spring	—	—	—	12.91	23.10	16.79	—	—	—	—	—	—	—	—	—
Blagoevgrad	Autumn	12.58	29.77	17.91	—	—	—	10.69	34.44	16.30	13.11	32.55	19.44	10.59	37.47	16.93
	Spring	—	—	—	10.28	33.57	15.63	—	—	—	—	—	—	—	—	—
Stanke Dimitrov	Autumn	11.93	37.90	19.21	—	—	—	12.03	32.68	18.76	11.81	36.60	18.65	12.33	32.90	18.37
	Spring	—	—	—	10.41	34.10	15.97	—	—	—	—	—	—	—	—	—
Kyustendil	Autumn	—	—	—	—	—	—	—	—	—	12.59	36.62	19.87	13.81	30.36	19.83
	Spring	—	—	—	11.59	29.14	16.36	—	—	—	—	—	—	—	—	—
Panagyurishte	Spring	10.66	25.69	14.34	13.80	24.28	18.22	—	—	—	13.91	22.78	18.14	13.17	22.96	17.10
Kazanluk	Spring	10.63	28.80	14.92	11.12	28.30	15.15	—	—	—	—	—	—	—	—	—
Pirdop	Spring	—	—	—	—	—	—	—	—	—	11.91	34.03	18.08	—	—	—
Ihtiman	Spring	10.44	30.82	15.09	13.24	27.20	18.18	—	—	—	12.65	30.19	18.12	—	—	—
Plovdiv	Spring	—	—	—	—	—	—	—	—	—	13.02	22.07	16.77	—	—	—
Peshtera	Spring	—	—	—	—	—	—	—	—	—	11.23	21.05	14.22	—	—	—
Pazardzhik	Spring	—	—	—	—	—	—	—	—	—	12.93	32.50	16.67	11.77	21.92	15.08
Isperikh	Spring	—	—	—	—	—	—	—	—	—	13.37	19.37	16.58	—	—	—
Popovo	Spring	—	—	—	—	—	—	—	—	—	13.52	20.75	17.06	—	—	—
Kubrat	Spring	—	—	—	—	—	—	—	—	—	12.84	20.97	16.25	—	—	—
Bela Slatina	Spring	—	—	—	—	—	—	—	—	—	11.74	22.01	13.34	—	—	—
Mihailovgrad	Spring	—	—	—	—	—	—	—	—	—	12.16	22.30	15.65	—	—	—
Tetrakan	Spring	—	—	—	—	—	—	—	—	—	13.83	13.19	16.39	—	—	—
Lom	Spring	10.01	31.00	15.88	—	—	—	—	—	—	11.60	16.04	13.82	—	—	—
Novi Pazar	Spring	—	—	—	—	—	—	—	—	—	11.17	28.67	15.66	—	—	—
	Mixed	—	—	—	—	—	—	13.38	20.40	16.81	—	—	—	—	—	—
Orekhovo	Spring	12.63	27.82	17.52	—	—	—	—	—	—	—	—	—	12.12	24.30	16.01

were taken from each part of the layer and placed in three jars; these were sealed and one was kept by ourselves, and one by the purchasing organization; one was put in the opium bank. When the opium was in the form of cakes, a proportional quantity of opium was taken from each cake, and a cut made along the radii of the cakes. The quantity thus obtained from the cakes was mixed in the manner described, until it became completely uniform. When the opium was both in cake form and in a form other than that of cakes, a general uniform mixture was again obtained according to the method described, and from this we finally took the average sample. The sample kept by ourselves was analysed. During these five years, we had no complaints about the analyses made. The results of analyses made by us according to the accepted lime method agreed with fair accuracy with the control analysis carried out in parallel by the Harrison Laboratory in London (for five samples, the differences were respectively +0.04%, +0.01%, −0.10%, +0.26% and −0.21%, or a mean difference of +0.0%) and also for the analysis carried out by the Vsesoyuz Khimeksport,* Moscow (with four samples, the differences were respectively −0.10%, −0.05%, −0.03% and +0.01% — again, the differences were quite small). A polarographic method for determining the morphine content of opium has also been worked out.

The procedure described in the above paragraph eliminates the effect of certain local factors on the taking of samples, such as the situation of the field, the height above sea level, the composition of the soil, the subsoil moisture, the slope of the field, and so forth. In all probability, the former method of taking samples from separate small holdings had an effect on the morphine content (14). The results of these researches have been published in the scientific transactions of the VMI (Higher Medical Institute), Sofia (vol. I, No. 2, 1954) (13). From this it appears that latitude, or even the general combination of climatic, soil and other conditions, does exert a certain influence on the quality of the opium obtained (15), but this influence is not considerable. The following places have accordingly been designated as the most suitable: Kyustendil, Sandanski, Stanke Dimitrov, Petrich, Blagoevgrad, Panagyurishte and some other districts in southern Bulgaria, while certain districts in northern Bulgaria, such as Popovo, Kubrat, Orekhovo and others, give quite good quality opium.

The results of these investigations are set out in table 3.

Our investigations showed that the southern regions were the most favourable for the cultivation of the poppy from the point of view of obtaining the best quality opium, but that good quality opium was also obtained in certain northern regions. The same investigations also showed that areas for opium cultivation were to be found in northern Bulgaria. It further appears that the variations in the composition of the opium from one and the same locality, district or region during different years are due to climatic conditions (13, 15, 16). The analysis results for opium obtained from spring sowings in certain regions were also of interest, especially when compared with the analysis results for opium obtained from the same regions from autumn poppies. Table 4 shows this comparison.

TABLE 4

Content of morphine in anhydrous opium depending on the time of sowing of the poppy

(In percentages)

District	Autumn poppy	Spring poppy	Difference
Petrich	18.18	16.79	1.39
Sandanski	18.51	16.79	1.72
Blagoevgrad	17.64	15.63	2.01
Stanke Dimitrov	18.74	15.79	2.95
Kyustendil	19.85	16.36	3.49
Panagyurishte	—	16.95	—
Pirdop	—	18.08	—
Kazanluk	—	15.03	—
Ihtiman	—	17.13	—
Plovdiv	—	16.77	—
Peshtera	—	14.22	—
Pazardzhik	—	15.87	—
Orekhovo mixed	16.82	16.76	0.06
Isperikh	—	16.58	—
Popovo	—	17.06	—
Kubrat	—	16.25	—
Bela Slatina	—	13.34	—
Mihailovgrad	—	15.65	—
Tutrakan	—	13.69	—
Lom	—	14.85	—
Novi Pazar	—	15.66	—

It is clear that the autumn sowings invariably give opium with a higher morphine content. The conclusion is that wherever the danger of the crop's freezing is small, because of the presence of snow cover or of the absence of low temperatures as a rule during the winter, it is always better to sow during the autumn. If, however, spring sowing is practised, the earlier it is done, the better the harvest.

Studies have been made simultaneously by us and by the research station at Sadovo to discover how opium and seed yield are affected by incision of the pods. The findings obtained from these tests are shown in table 5.

The results of these tests show that with increase in the number of incisions above the poppy capsule, the yield of crude opium is increased by 14.3% with two incisions, and by 21.1% with three incisions, as against the single incision performed in the control experiment.

The quantity of seed obtained in each experiment when incision was performed was less than that obtained from the non-incised capsules (a 5.3% reduction in the seed yield with one incision as compared with the non-incised poppy; a 7.4% reduction with two incisions as compared with a single incision, or 12.7% as compared with the non-incised poppy; a 12.3% reduction with three incisions as compared with a single incision, or 17.6% as compared with the non-incised capsules).

* Vsesoyuznyi ob edinenie po eksportn i importn khimicheskikh i meditsinskych tovorov (All-Union Corporation for the Import and Export of Chemical and Medicinal Goods).

TABLE 5

Effect of the number of incisions of the poppy capsules on the opium and seed yield

Serial No.	Number of incisions	Yield						
		Crude opium					Seed	
		Kg per decare	%	% morphine 1952	% morphine 1953	% morphine 1954	Kg per decare	%
1	No incisions	—	—	—	—	—	30.0	105.3
2	Incisions	0.280	100.0	19.58	19.49	12.45	30.0	100.0
3	Incisions	0.320	114.3	17.88	19.75	12.51	28.5	92.6
4	Incisions	0.340	121.1	—	19.64	12.12	25.0	87.7

A particularly important condition for high opium yield is that the poppy capsules should be incised, and the opium collected as soon as the appropriate moment occurs. Table 6 shows the results of a test made in this connexion.

TABLE 6

Influence of the time of incision of the poppy capsules on opium and seed yield (spring poppy, 1954)

Serial No.	Date of incision	Crude opium		Seed	
		Kg per decare	%	Kg per decare	%
1	21 June	0.240	75.0	23.0	98.5
2	26 June	0.320	100.0	26.0	100.0
3	30 June	0.280	87.5	26.2	100.8
4	4 July	0.160	50.0	26.5	100.9

During this experiment the poppy capsules themselves underwent visible changes during the days around 26 June, and these changes made it possible to determine the most favourable moment for making the incision ("industrial maturity") according to the outward signs described above: the poppy capsules acquire a grey colour with a bronze lustre, and the "sides" of the capsule become stronger, showing a very characteristic whitish-coffee-coloured ring under the capsule itself.

Making the incision during the period of industrial maturity ensures the maximum opium yield and the minimum reduction in seed yield, as compared with later incision. Making the incision either before or after industrial maturity leads to a noticeable reduction in the opium yield. Premature incision causes a 25% reduction in opium yield, while if the incision is made after industrial maturity, the yield is reduced by 12.5% if four days have elapsed, and by 50% if eight days have elapsed. As can be seen from the table, the increase in seed yield when the incision is delayed is at the very least 0.8% or 0.9%.

Consequently, it is imperative to make the incision of the poppy capsules during the exact period of industrial maturity and after the signs described above have been noted.

Tests have also been made to determine the influence of incisions made at various times during the day. The results are shown in table 7.

The following conclusions can be drawn from the experiments.

A certain increase in the quantity of opium is observed when the incision of the poppy is made during the hottest hours of the day (the optimum quantity is obtained at 2 p.m.), and a certain diminution when it is made during the earlier and later hours of the day. The quantity is lowest when the incision is made early in the day.

TABLE 7

Opium and seed yield as affected by the time of day at which the incision is made

Time of day	Kg per decare	1954 and later crop					1952/53 crop		
		Crude opium				Seed	Crude opium		
		%	% morphine	% moisture	% morphine in dried substance	Kg per decare	% morphine	% moisture	% morphine in dried substance
8 a.m.	0.290	90.6	8.67	26.92	11.81	28.8	15.23	26.75	20.79
10 a.m.	0.300	93.7	8.71	27.98	12.10	26.8	16.22	29.71	22.98
Noon	0.320	100.0	8.87	32.25	13.10	26.8	17.77	28.98	27.99
2 p.m.	0.325	101.6	10.02	18.79	12.37	26.8	16.52	33.23	27.77
4 p.m.	0.310	97.0	11.25	17.25	13.12	26.8	17.88	22.98	23.22
6 p.m.	0.300	93.7	13.12	22.53	18.23	26.8	15.27	31.17	22.18

The time of day at which the incision is made also affects the percentage of morphine content in the opium. During the early hours of the day (8 a.m. to 10 a.m.), the opium obtained had a low percentage content in morphine, while the quantity increased during the hotter hours (noon to 4 p.m.). Investigations made by Milov, Nilov & Troshchenko in 1936 (17) show that the morphine content in the milky juice decreases exceptionally quickly when the juice is left standing in the open air. The main reason for this lies in the acidification processes which occur as a result of oxidation and peroxidation. Proceeding from this fact, the authors used various decoctions for the ferments, by means of which the process of morphine disintegration was considerably reduced. The substances acted as preserving media. It was considered to be worth establishing a similar process for Bulgarian opium.

Various preservative substances mentioned in the literature were used, although the method for their application is not indicated in the works concerned. We took samples of the milky juice and opium under different conditions of incision, collection and storing of samples, working with poppies taken from the same field. Samples preserved according to the method indicated below were kept in sealed jars for two years before being analysed.

The results are shown in tables 8, 9 and 10.

It can be seen from the experiment that when the milky juice is left to stand above the poppy head, a considerable portion of the morphine is lost. In our test this loss amounted to 36.13%. The result was similar to that obtained in the tests made by Nilov & Troshchenko. We obtained similar results with other tests also, when the analysis was made on the day when the milky juice and the opium were collected.

In order to establish the preservative action of certain chemicals, samples were taken from a few grammes taken under identical conditions of cutting, collection and storing. To each sample we added 0.2 g respectively of calcium fluoride, aniline hydrochloride, calcium cyanide, hydroxylamine hydrochloride and sodium chloride, while one sample was treated in the classic manner for opium production. This then served as a standard. We mixed the chemicals by agitating thoroughly with a glass rod immediately after the milky juice had been collected. The analysis results from these tests are shown in table 9.

TABLE 8

Sample	Percentage of morphine	Percentage of moisture	Percentage of morphine in dry substance
Milky juice collected immediately after cutting of the poppy head .	5.84	64.62	16.50
Normal standard sample of opium (milky juice collected on the following days)	3.73	63.14	10.12

TABLE 9

Test	Percentage of morphine	Percentage of moisture	Percentage of morphine in dry substance
Normal (standard)	8.05	44.80	14.58
Calcium fluoride	7.44	46.87	14.00
Aniline hydrochloride	7.85	42.71	13.70
Calcium cyanide	7.94	46.40	14.81
Hydroxylamine hydrochloride ...	7.85	47.00	14.81
Sodium chloride	8.25	47.43	15.69

TABLE 10

Sample No.	Method of taking sample	In the presence of moisture			After drying at 40° C		
		Percentage of morphine	Percentage of moisture	Percentage of morphine in dry substance	Percentage of morphine	Percentage of moisture	Percentage of morphine in dry substance
1	2	3	4	5	6	7	8
I	Standard	13.30 8.05	26.16 44.80	14.11 14.58	14.33 14.52	7.2 7.38	15.44 15.67
II	Poppy heads wetted with a solution of sodium hydrosulphide before cutting	14.11	62.50	10.96	12.61	7.9	13.7
III	Poppy heads wetted with a solution of sodium hydrosulphide after cutting	6.23	62.08	11.16	13.65	6.94	14.66
IV	0.20 g sodium hydrosulphide added after the opium was collected in the normal manner	4.50	64.16	12.56	14.20	7.38	15.33
V	Knife dipped in solution of hydroxylamine hydrochloride during cutting of the poppy head	12.16	18.46	14.91	—	—	—
VI	Knife dipped in solution of sodium chloride during cutting of poppy head	11.42	29.10	16.10	15.43	7.35	16.65
VII	Knife dipped in solution of sodium nitride during cutting of poppy head	15.74	8.45	17.17	—	—	—

Analyses were also made on a standard sample directly with the presence of moisture, and on a standard sample after primary drying at 40°C to a pre-determined moisture content. Samples obtained from poppy heads which had been wetted with solutions of various preservative media immediately after the poppy capsules had been cut were analysed in the presence of moisture and after primary drying at 40°C.

The results of these tests are shown in table 10.

It can be seen from the analysis of the figures that sodium chloride and sodium nitride are good preservative media for Bulgarian opium. The easily obtainable common salt, which is cheap, and available in every household, deserves special attention in this connexion. There is need for further work along these lines.

Alkaloids in Poppy Capsules

Opium production is fairly laborious work, and calls for skilled labour. Its promotion to the rank of an intensive crop has meant that a considerable additional part of the labour force in our rural areas is engaged in producing it, and this occurs at the very time when the poppy reaches industrial maturity. This makes it difficult to produce the opium required for the pharmaceutical industry and for export, as well as to produce the opium alkaloids.

For this reason, we have moved in the direction of isolating morphine not only from opium, but also from the poppy plant itself.

Comparative studies were made on the basis of the commonly accepted postulates and on the known methods suggested for isolating morphine from the poppy capsule (18). From these studies, it has been found that Kabay's method — which was until recently the most frequently suggested — and its modification according to Bognar (19), have the disadvantage that large quantities of the solvent (water, alcohol) evaporate under comparatively easy conditions (vacuum). A method which we have worked out for extracting the alkaloids by means of chloroform on a perforated grid base gives good results.

Of late, there has been a considerable development in the mixture of synthetic ion-exchange resins. These are steadily replacing the classic methods of isolating different plant substances. In Bulgaria, the Soviet method for isolating morphine from the poppy capsules by means of such a resin (Vofatite F) has been introduced.

In connexion with the above, we append notes on certain questions relating to the morphine content in the dried poppy capsules, incised and non-incised, obtained at various places in Bulgaria.

Research has been carried out in respect of the morphine content in the capsules of poppies cultivated in Bulgaria, after the seed has been collected. Incised and non-incised poppy capsules were analysed (20). The results are shown in table 11.

TABLE 11

Quantitative morphine content in samples of dried poppy capsules, incised and non-incised from various places in Bulgaria. 1955 harvest

Serial No.	Number of samples	Locality	District	Whether incised or not	% moisture	% morphine	Comments
1	1	Kavrakirovo	Petrich	Yes	8.66	0.395	—
2	7	Mikrovo	Sandanski	Yes	5.70	0.425	—
3	9	Sklave	Sandanski	Yes	5.30	0.375	—
4	11	Lozenitsa	Sandanski	Yes	2.25	0.40	—
5	13	Khotovoi ..... Spatovo	Sandanski ..... Sandanski	Yes	6.6	0.425	—
6	14	Sandanski (town)	Sandanski	Prelim. inc.	6.15	0.35	—
7	10	Lazarevo	Sandanski	No	5.45	0.53	—
8	12	Sandanski (town) ..... Dzhugorovo ..... Polenitsa	Sandanski	No	5.60	0.535	—
9	3	Khursovo	Blagoevgrad	Yes	6.40	0.41	—
10	4	Khursovo	Blagoevgrad	Yes	5.5	0.308	with 4-5 cm spathe
11	2b	Leshko	Blagoevgrad	Yes	7.08	0.37	—
12	2a	Leshko	Blagoevgrad	No	6.3	0.425	—
13	8	Blageovgrad (town)	Blagoevgrad	Prelim. inc.	7.3	0.333	—
14	6	Dzherman	Stanke Dimitrov ...	Yes	5.9	0.34	—
15	5	Dzherman	Stanke Dimitrov ...	No	4.5	0.408	—

On the basis of these investigations as well as of earlier research, the following main conclusions could be drawn.

1. The poppy grown in Bulgaria yields dry capsules with a morphine content which is among the highest in the world.

2. No significant difference has been noted with regard to morphine content in sample capsules obtained from different parts of the country.

3. Given favourable conditions (experienced labour force and dry warm weather during the period of industrial maturity), it is recommended that the opium be collected, and after this the dried incised capsules; the seed is subsequently collected, so that the morphine and other alkaloids can be isolated.

In order to improve, if possible, the methods for isolating the morphine from the dried capsules through absorption, we carried out an investigation to establish the volume of some synthetic resins in relation to morphine hydrochloride. Comparative studies were made with the following resins: Vofatite KPS 200, Vofatite F, Vofatite P, Vofatite CN, Vofatite ND, Vofatite L.150, Vofatite L.165, Vofatite E, to establish the volume of these both under air drying conditions and when the sample was dried at 100 to 105°C and at 120°C. The results of these investigations are shown in table 12.

With some of the resins, the influence of the dropping rate on the volume of the absorbent (21) was also studied. Results are shown in table 13.

Certain conclusions can be drawn from the tests which have been made.

1. It was found that all the cationites and anionites have the greatest total volume when they are air-dried, with the exception of Vofatite KPS200, which has a slightly increased volume after drying at 100-105°.

2. The total volume of the cationites and anionites is small after drying at 100-105°, and is still smaller after drying at 120°.

3. An exception is Vofatite KPS 200, which has its greatest volume, in comparison with all the other Vofatites studied, when dried at 100-105° and even at 120°. The volume of the air-dried resin KPS 200 is less by almost a half. Vofatite KPS 200 dried at 100-105° possesses almost the same volume as it does when dried at 120°. This Vofatite has the greatest total volume of all the Vofatites studied.

4. Vofatite CN has the lowest total volume, practically equal to 0.

5. It can be seen from the tables that the dropping rate greatly affects both the total volume, and also the volume, before opening, of the cationite Vofatites P and F before, since with slow dropping the volume is considerably greater. The volume is much greater with Vofatite P.

6. With Vofatite MD the difference is much more considerable, both as regards the air-dried substance and as regards the substance heated at 120°.

Research for the purpose of separating morphine from the dry poppy capsules by means of the above-mentioned absorbants is being continued.

TABLE 12

Form of Vofatite absorbent	Air dried			Dried at 100-105°			Heated at 120°		
	% before opening	% after opening	Total volume	% before opening	% after opening	Total volume	% before opening	% after opening	Total volume
KPS 200	60.04	2.67	64.71	82.69	38.87	121.56	98.08	21.98	120.06
F	8.02	39.23	47.25	8.76	19.54	28.30	1.92	9.28	11.20
P	10.33	8.91	19.24	5.7	10.71	16.41	7.48	6.43	13.91
CN	0	0	0	0	0	0	0	0	0
ND	—	—	15.99	—	—	11.60	—	—	8.91
L. 150	—	—	47.61	—	—	36.26	—	—	29.39
L. 165	—	—	48.78	—	—	53.02	—	—	29.39
E	28.56	27.81	56.37	5.82	1.24	7.06	4.13	1.61	5.74

TABLE 13

Form of absorbent	Dropping rate	Air Drying			Heated at 120°		
		% before opening	% after opening	Total volume	% before opening	% after opening	Total volume
Vofatite P	1 drop/4-5 sec.	54	19.3	73.3	39.5	8.3	47.8
	1.15 drop/1 sec.	10.33	8.91	19.24	7.48	6.43	13.91
Vofatite F	1 drop/4-5 sec.	57	5	62	42.2	6.4	48.6
	1.15 drop/1 sec.	8.02	39.23	47.25	1.92	9.28	11.23
Vofatite ND	1 drop/4-5 sec.	—	—	19.75	—	—	13.71
	1.15 drop/1 sec.	—	—	15.99	—	—	8.91

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The work of the Permanent Central Opium Board in 1959

The Annual Report of the Permanent Central Opium Board to the Economic and Social Council on its work has been a perennial item on the agenda of both the Council and the Commission on Narcotic Drugs. The report on the Board's work in 1959 [1] presents an over-all picture of the legal trade in narcotics throughout the world in 1958, derived from the statistics submitted to the Board by governments in pursuance of the international conventions of 19 February 1925 and 13 July 1931 and of the Protocol of 19 November 1948. Extracts of the chapter of this report entitled: " Trends in the licit movement of narcotic drugs in 1958 " follow.

Raw materials

Raw Opium. — The demand for opium for medical purposes almost doubled between 1948 and 1958, whereas licit consumption for quasi-medical and non-medical purposes fell by five-sixths. In 1948, this consumption absorbed over one-third (270 tons) of the total amount of opium used for licit purposes (740 tons); in 1958, it dropped to 46 tons and accounted for no more than one-twentieth of the total, which rose to 944 tons.

Opium is above all the raw material of codeine, which is the most widely used of its derivatives, so that the two substances follow a similar trend. Thus, the fact that the demand for opium for medical purposes increased from 465 tons in 1948 to 898 tons in 1958 was due to the continuous rise in the consumption of codeine. As regards licit quasi-medical and non-medical consumption the decline was due to the Government of India's decision gradually to curtail such consumption with a view to total elimination in 1959. Opium smoking was licit in Thailand in 1958, and 19 tons of raw opium were utilized for this purpose during that year.

In 1958 India contributed more than two-thirds (657 tons) of the world production of opium (939 tons). The remainder was shared by Turkey (162 tons), the USSR (93 tons) and four other countries, Yugoslavia, Pakistan, Japan and Bulgaria, with a total of 27 tons. As compared with 1948, production in 1958 almost doubled in India and increased by one-quarter in the USSR, whereas it fell by more than one-half in Turkey. It will be remembered that production in Iran ceased in 1955.

The figures for production and use of opium, expressed in terms of a common moisture content, show a shortfall in production since 1954, the difference between the two totals being, however, smaller in 1958 than in 1957. In consequence, stocks which at the beginning of 1954 were 1,744 tons fell by the end of 1957 to 948 tons and by the end of 1958 to about 840 tons, or nine months' requirements.

Poppy straw. — In 1958, one-fifth (i.e., 22 tons) of the morphine produced was extracted from poppy straw. The total for 1958 thus exceeds the previous peak figure reached in 1954, which was 20 tons, or one-fourth of the total production of morphine.

During the period 1954-1958, the decrease in the manufacture of morphine by this process in the Federal Republic of Germany, France and Czechoslovakia was more than balanced by an increase in the Netherlands, Hungary, Poland and the German Democratic Republic, which have long been using it, and in the USSR and Romania, where it was introduced in 1957.

Coca leaves. — None of the three main coca-leaf producing and consuming countries, Peru, Bolivia and Colombia, have supplied the Board with the relevant statistics for 1958. Their reported total production amounted to 13,000 tons in 1954 and again in 1957. By comparison, the quantity harvested in the other two known producing countries, Indonesia and the Republic of China, is negligible, amounting respectively to only 8 tons and 1.5 tons in 1958.

Medical requirements of coca leaves — that is to say, their use in the licit manufacture of cocaine — fell from 588 tons in 1954 to 248 tons in 1957 and 205 tons in 1958. In 1957 they represented only 2 per cent of licit non-medical consumption, and the proportion must be even smaller in 1958.

According to information supplied by the governments concerned, the following quantities of coca leaves were licitly consumed for non-medical purposes, that is to say, were chewed during the period 1954 to 1958:

	1954	1955	1956 (tons)	1957	1958
Peru	9 250	9 319	9 450	9 954	?
Bolivia	2 764	?	?	2 590	?
Argentina	129	155	14	152	80
Colombia	110	100	80	32	?

Cannabis. — The medical and quasi-medical use of cannabis is very small and has diminished from 862 kg in 1954 to 559 kg in 1957. The reduction in 1958 cannot be computed since India, which has the largest consumption (136 kg in 1957), has not yet furnished the relevant statistics.

Manufactured drugs

Morphine. — The appreciable rise in morphine production which was observed between 1956 and 1957, from 87 to 109 tons, slowed down in 1958, the total for that year exceeding that for 1957 by only 3 tons. This merely reflects the trend in the conversion of morphine into other drugs, chiefly codeine: 85 tons in 1956, 103 tons in 1957 and 105 tons in 1958. In 1957 as in 1958, the figures for both production and conversion are double those for 1948. On the other hand, the consumption of morphine as such (about 4 tons in 1958 as against 6 tons in 1948) is on the decline.

[1] Document E/OB/15, November 1959.

Although production hardly varied from 1957 to 1958 it nevertheless fell by 3.4 tons in three of the five countries producing 10 or more tons of morphine each per year, namely, the United States, the United Kingdom and France, a reduction which was offset by an equivalent increase in the other two countries, the USSR and the Federal Republic of Germany. In all these countries variations in production merely reflect changes in the demand for drugs manufactured from morphine.

Diacetylmorphine. — The position with regard to this drug hardly changed in 1958, except that none was manufactured in France. Production continued in the United Kingdom (57 kg) and in Belgium (11 kg) and was resumed in the Netherlands (2 kg).

In the United Kingdom 48 kg of diacetylmorphine were consumed in 1958 and 20 kg were used for manufacturing nalorphine, a non-addiction-producing substance. In Belgium all but 1 kg of the diacetylmorphine produced was consumed in the country; in the Netherlands it was added to stock. This drug has practically vanished from the international trade, so that consuming countries which do not manufacture it have had to draw on their stocks. Their consumption figures in 1958, where these amounted to 1 kg or more, were: 4 kg in France, 3 kg in Canada, 2 kg in Portugal, 1 kg each in Australia, Italy and Uruguay.

Codeine. — From 1956 to 1957 codeine consumption underwent an exceptional increase (from 77 to 90 tons), which was attributed to the worldwide influenza epidemic. The final total for 1958 will approach that for 1957. Manufacture more than kept pace with this increase, having risen from 80 tons in 1956 to 97 tons in 1957 and to 100 tons in 1958. Excess production was added to stock.

Ethylmorphine. — Consumption which rose from 6.2 tons in 1956 to 7.1 tons in 1957, fell back to 6.4 tons in 1958, whereas the quantities manufactured were 5.5 tons, 7.4 tons and 7.8 tons respectively.

Other derivatives of opium alkaloids. — Except for hydromorphone and dihydromorphine, the demand for all these narcotic drugs has risen appreciably since 1954. In 1958 the following quantities were produced: Dihydrocodeine 2,442 kg, Hydrocodone 1,432 kg, Pholcodine 1,215 kg, Oxycodone 464 kg, Thebacon 188 kg, Benzylmorphine 102 kg, Hydromorphone 94 kg, Dihydromorphine 22 kg, Acetyldihydrocodeine 6 kg, Nicomorphine 2 kg, Oxymorphone 1 kg.

Cocaine. — Cocaine consumption decreased by one-quarter in the past five years (from 2 tons in 1954 to 1.5 ton in 1958). Production shows a similar though less regular trend. In 1958 it was about the same as consumption.

Pethidine. — The annual consumption of pethidine has remained steady at between 13 and 14 tons since 1955, the United States share of the total varying between 8 and 9 tons. Between 1955 and 1957, annual production was nearly 15 tons; in 1958 it dropped to 13 tons.

Trimeperidine. — This narcotic drug is manufactured and consumed only in the USSR. 1,078 kg were produced in 1958.

Normethadone. — The Federal Republic of Germany is the largest consumer of this drug as well as the largest producer and exporter. (Last information: 1,571 kg produced in 1956.)

Methadone. — The consumption of methadone has been declining from 570 kg in 1954 to 445 kg in 1958.

Racemoramide, dextromoramide and levomoramide. — In 1958 the Netherlands produced 457 kg of racemoramide of which 414 kg were used for manufacturing 147 kg of dextromoramide and 140 kg of levomoramide. In view of this apparently low yield it must be presumed that the manufacturing process was not completed by the end of 1958. Three kilogrammes of dextromoramide were manufactured in Italy.

In 1958 the following countries reported a consumption of at least 1 kg of dextromoramide; France 57 kg, Belgium 13 kg, Argentina 12 kg, Sweden 11 kg, Spain 8 kg, Finland 4 kg, Netherlands 4 kg, Denmark, Italy and Switzerland 2 kg each.

Ketobemidone. — The over-all consumption of this drug shows no appreciable change: 74 kg were consumed in 1958.

Denmark and Switzerland are still the only producers. Denmark produced 32 kg and Switzerland 34 kg in 1958.

Other synthetic narcotic drugs. — Last year the 1957 statistics showed that none of these drugs was yet manufactured in large quantity or consumed in many countries; the figures for 1958 indicate that this conclusion remains valid except as regards anileridine. This drug is now being manufactured in quite large quantities, but it is consumed only in the United States and Canada (455 kg in 1958).

Consumption

Narcotic drugs derived from opium retain their lead both as analgesics and as antitussives. As analgesics, however, their use shows a steady downward trend, while as antitussives it is moving steeply upward.

The use of synthetic narcotic drugs as analgesics has grown. Although it is not possible to follow the trends of synthetic antitussives it can be said that their use is negligible in comparison with that of antitussives derived from opium.

Estimated world requirements of narcotic drugs in 1960

In pursuance of the International Convention of 13 July 1931, the Drug Supervisory Body publishes an annual statement of estimated world requirements of narcotic drugs. This statement also includes estimates for the narcotic drugs brought under international control by virtue of the Protocol of 19 November 1948.[1] Extracts from this statement for 1960 follow.

Operation of the estimates system

In accordance with the provisions of the 1931 Convention, the estimates accepted by the Supervisory Body are used by the Permanent Central Opium Board in the calculation of manufacture and import limits for each country or territory and for each drug. It is therefore essential that the estimates should reflect requirements as faithfully as possible.

Receipt of estimates for 1960

Ninety-five countries and 84 non-metropolitan territories are shown in the statement for 1960. At the time when it was drawn up, estimates for 1960 had been received from 90 countries and 71 non-metropolitan territories. In the case of countries and territories for which no estimates have been received, it is the duty of the Supervisory Body, under the 1931 Convention, to establish them itself, and thereby ensure the universal application of the estimates system. The Supervisory Body has accordingly established estimates for 1960 in respect of 5 countries and 13 non-metropolitan territories.

World totals of estimates from 1954 to 1960

The figures shown in table 1 are for each drug, the sum of the "Total of the Estimates" defined in article 5, paragraph 2, of the 1931 Convention,[2] of all the countries and territories in the world, provided they reached 1 kg in any one of the five years considered. The 1960 figures will be modified by supplementary or amended estimates received up to the end of the year.

[1] Document E/DSB/17.

[2] Article 5, paragraph 2, reads in part:

(*a*) The quantity necessary for use as such for medical and scientific needs, including the quantity required for the manufacture of preparations for the export of which export authorizations are not required, whether such preparations are intended for domestic consumption or for export;

(*b*) The quantity necessary for the purpose of conversion, whether for domestic consumption or for export.

The total of the estimates for each country or territory shall consist of the sum of the amounts specified under (*a*) and (*b*) of this paragraph. With the addition of any amounts which may be necessary to bring the reserve stocks and the government stocks up to the desired level, or after deduction of any amounts by which those stocks may exceed that level.

TABLE 1

Drug	1954	1955	1956	1957	1958	1959	1960
	kg.	kg.	kg.	kg.	kg.	kg.	kg.
Benzylmorphine	60	100	100	138	141	150	86
Cocaine	4 822	3 797	3 028	2 778	2 891	2 581	2 027
Desomorphine	3	2	2	2	2	1	1
Diacetylmorphine	338	259	176	141	123	104	90
Dihydromorphine	6	4	24	14	11	11	3
Ecgonine	—	—	—	2	—	—	—
Ecgonine methyl ester	—	1	—	32	53	110	20
Hydrocodone	1 012	949	1 318	1 459	1 587	1 568	1 493
Hydromorphone	212	201	164	202	236	165	130
Metopon	2	5	4	3	3	3	5
Morphine	103 235	105 589	100 594	111 237	123 135	119 385	123 510
Morphine-N-oxide	2	1	1	—	—	—	—
Nicomorphine	—	—	—	—	2	13	7
Normorphine	—	—	—	—	—	3	—
Oxycodone	688	577	544	601	770	724	595
Oxymorphone	—	6	6	5	4	7	15
Thebacon	209	181	180	183	182	151	154
Thebaine	3 219	3 228	3 372	4 572	4 589	3 769	3 099
Acetyldihydrocodeine	49	50	10	14	17	20	12
Codeine	94 940	99 065	94 225	105 639	106 609	110 853	106 621
Dihydrocodeine	1 159	1 483	1 806	1 816	2 621	3 720	3 213
Ethylmorphine	9 730	9 667	9 024	10 230	9 225	10 554	8 499
Pholcodine	1 141	1 184	1 085	1 320	1 646	1 506	1 316
Acetylmethadol	2	1	1	—	—	—	—
Alphaprodine	70	90	84	75	77	68	57
Anileridine	—	—	—	717	886	1 078	840
Betameprodine	20	3	2	—	—	—	—

(Continued overleaf)

TABLE 1 *(continued)*

Drug	1954	1955	1956	1957	1958	1959	1960
	kg.	kg.	kg.	kg.	kg.	kg.	kg.
Betaprodine	2	2	10	8	—	—	—
Dextromoramide	—	—	—	126	535	759	383
Diethylthiambutene	—	—	17	27	19	17	12
Dimepheptanol	6	2	2	—	1	—	—
Dimethylthiambutene	—	3	4	2	6	1	1
Dioxaphetyl butyrate	—	—	—	2	2	2	1
Dipipanone	40	5	19	10	53	108	65
Ethylmethylthiambutene	—	1	1	2	—	1	—
Etoxeridine	—	—	—	—	31	13	6
Hydroxypethidine	1	2	2	—	—	—	—
Isomethadone	66	19	18	18	21	9	8
Ketobemidone	235	175	92	85	136	104	64
Levomethorphan	2	2	2	—	—	—	—
Levomoramide	—	—	—	—	—	196	—
Levorphanol	138	170	122	156	92	91	48
Methadone	792	900	691	906	769	852	652
Normethadone	—	30	107	198	286	290	408
Pethidine	19 947	17 927	16 328	17 994	17 216	18 162	16 293
Phenadoxone	194	134	105	82	65	40	34
Phenazocine	—	—	—	—	—	20	65
Properidine	—	1	65	41	35	27	18
Racemethorphan	—	2	2	—	—	—	—
Racemoramide	—	—	—	—	—	7	—
Racemorphan	85	5	3	3	4	4	—
Trimeperidine	—	—	—	—	1 150	1 200	1 400

A note on the identification of dimenoxadol

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Recently, the United Nations Expert Committee on Addiction-producing Drugs (1) decided that dimenoxadol (dimethylamino-ethyl-1-ethoxy-1,1-diphenylacetate) was a substance liable to cause addiction, and recommended that it should be brought under international control. When a drug is proscribed in this manner, its identification becomes a matter of considerable importance. Tests for a large number of synthetic analgesics have recently been published (2).

Microgram quantities of dimenoxadol may readily be identified by crystal and colour tests, using the micro-techniques developed by Clarke & Williams (3, 4). As is the case with other compounds containing the benzhydryloxy grouping, it gives a bright orange-yellow colour with all the concentrated sulphuric acid reagents. With most of these reagents, this colour fades rapidly, but with the Marquis reagent (formaldehyde/sulphuric acid), it changes to a bright blue-green. Although this is a distinctive and delicate test, the sensitivity being of the order of 0.1 μg, it is not specific, since benactyzine, lachesine, and poldine give a similar colour sequence (5).

Final identification may, however, be made by means of crystal tests, as dimenoxadol forms typical crystals with a number of alkaloidal precipitating reagents. Thus with styphnic acid, it forms bunches of irregular plates; with platinum bromide, rosettes of branching rods; with picrolonic acid, small rosettes of rods and needles; with platinum chloride, small dense rosettes; with lead iodide, rectangular plates; and with mercuric chloride, transparent rhomboids. The first two tests are the most delicate, having a sensitivity of about 0.01 μg. The test with mercuric chloride is highly characteristic, but is not very sensitive (0.25 μg), and the crystals form very slowly, sometimes not for twenty-four hours.

I am most grateful to Dr. Nathan B. Eddy of the National Institutes of Health, Bethesda, Md., for a gift of this compound.

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